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Special Issue on

CRISPR and Genome Editing: Impacts and Implications

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Editorial Introduction

K. Ravi Srinivas*

As we all know that Genome Editing has emerged as a key topic in bio and life sciences on account of various factors. The last year's recognition of the importance of CRISPR/genome editing by awarding Nobel Prize in Chemistry to Emmanuelle Charpentier Max Planck Unit for the Science of Pathogens, Berlin, Germany, and, Jennifer A. Doudna, University of California, Berkeley, USA , "for the development of a method for genome editing" is yet another proof of the importance of CRISPR/genome editing. Last year RIS organised a webinar on 'Nobel Prize for CRISPR'. This Special Issue is based to a great extent on the talks/presentations made in the webinar. This issue carries four papers, a 'Perspective' paper and two book reviews.

Mapping of human genome and related developments opened up new ways to understand genetic diseases and find enduring cures to them. Thanks to developments in bioinformatics, genomics and related disciplines today finding solutions to vexing issues and diseases has been made possible, even as they result in tricky problems for policy making and raise concerns related to ethics and ethical use of technologies, applications, and similar options. Gene therapy for instance is closer to adoption at a large scale now, at least technically. In their paper, B.K.Thelma and Yadav explain in detail the how CRISPR/Cas9 based genome editing tool can be used to correct a disease causing mutation in somatic/gene cells. They further illustrate this with a clinical application, Human heritable genome editing (HHGE) in combination with Assisted Reproduction technology and Pre-implantation diagnostics. They examine the benefits, potential risks and limitations and highlight how this application can be useful in some cases where there are no other viable technological options or medical interventions are available. They highlight the ethical issues that arise on account of HHGE

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and the concerns over regulation and adoption of this. HHGE is an exciting option and the opinion on this is divided with demands from outright ban to adoption on a large scale with proper regulation, and, there are positions that are in between these two extreme approaches.[1]. The paper by Thelma and Yadav is a contribution to the global debate on this issue.

Obviously, translational governance of genome editing, particularly HHGE is not only a matter of debate but also is a wicked problem. Although National Academy of Sciences and other similar institutions and World Health Organizations are working on this, neither consensus nor a legally binding convention or treaty is in the offing. While national regulations are necessary, they are not sufficient as what is banned/regulated in one country/region might well be available without restrictions in (an)other country/ies. Andrea Boggio proposes an approach based on a model legislation to regulate HHGE. While he agrees that consensus may be difficult to arrive at, he opines that using a law and relevant guidelines at the national level based on a model law can be an important starting point. Obviously harmonisation in this may not occur while convergence can happen. On the other hand, a model law can stimulate novelty in national regulation which can result in regulation with flexibilities and certain prohibitions. In case of HHGE despite objections on moral and ethical grounds, there are stakeholders who see a ray of hope in HHGE when no other option is available. So if one considers the complexities in governance and lack of consensus in regulating HHGE his approach can be considered as a pragmatic approach worth considering.

But is ethics in genome editing just a buzz word or catch all phrase or is used to scare people against its applications particularly HHGE. Although it may appear so superficially, the reality in different. Various committee are working on this and there is considerable literature on this by now. Drawing upon the global debates, and ethical principles Roli Mathur calls for building bridges between science and society, using ethical values and frameworks. Her paper underscores the need for actions and initiatives on many fronts and outlines what all can be done. She provides insights for developing regulatory frameworks and cites relevant examples including National guideline document on gene therapy in India. The paper by Andrea Boggio and Roli Mathur complement each other as they discuss approaches

to human genome editing that are necessary so that while governance reflects ethics and societal values, the application of technology enables enjoying the fruits of science and technology and is backed by appropriate legal frameworks. Roli Mathur calls for a multipronged approach that goes beyond investing in Science and Technology and implementing such an approach is a challenge but doable.

Poorti Kathpalia and Debojyoti Chakraborty in the paper by them trace the developments in CRISPR technology and show how it has become so important, highlighting its potentials and current applications in different fields. More importantly they also point out that there are technical challenges in making CRISPR a better suited and more relevant tool. The COVID Pandemic necessitated the development of reliable testing methods and diagnostics that could be deployed in a large scale and with reliable results with the requisite sensitivity so that there are no misleading results. Taking this as an example they have written how CRISPR enabled addressing this problem successfully, and how many diagnostic kits/methods like FELUDA were developed in a short time. That is a remarkable achievement and Poorti Kathpalia and Debojyoti Chakraborty had played major roles in developing of FELUDA[2]. FELUDA is an acronym for (FnCas9 Editor Linked Uniform Detection Assay), and the name is inspired by a popular character immortalized by Satyajit Ray in his tales of mystery.

The need to take a comprehensive approach to genome editing particularly from an ethical perspective is obvious and this should go beyond HHGE. European Group on Ethics in Science and New Technologies (EGE) has developed one such approach with recommendations and has included Gene Drives in that. The summary of its findings and recommendations are provided as 'Perspectives'. While EGE has a specific mandate and examines issues taking into account European values and fundamental rights, its findings have wider relevance. As Europe is a major stakeholder in innovation and governance, perspective of EGE is important. Read with the paper by Andrea Boggio it will give an idea on governing an emerging technology which has enormous ethical implications and practical applications.

The issue carries two book reviews which add value and diversity. Given the complex nature of the themes and topics covered in this issue and the need to understand the science behind them is obvious. Hence papers that carry scientific information have been published in this issue. Even if the scientific component is not understood in the first reading, we request readers not to give up on reading them and try to understand them. In any case there is much material is available for popular understanding on these issues and these can also be read as supplementary sources of information and for enhanced understanding.

In future we will be publishing more on CRISPR/Genome Editing, besides organising events including webinars. Your views and suggestion on this issue and on ABDR are welcomed.

Endnotes

[1] See for example Baxter, J. When is it Safe to Edit the Human Germline?. Sci Eng Ethics 27, 43 (2021). https://doi.org/10.1007/s11948-021-00320-x

[2] https://tigs.res.in/2021/03/15/the-making-of-csir-igibs-feluda/

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Human Heritable Genome Editing – Potential and Current Status for Clinical Use

Navneesh Yadav and B. K. Thelma*

Abstract: Medical genomics has moved significantly from human genome sequencing project uncovering millions of variations across the genome to identifying disease specific variants in a substantial number of human genetic disorders. Understanding the molecular basis of single gene disorders (SGDs) in particular, has opened up possibilities of i) notable prediction and prevention with powerful diagnostic tool development and ii) improved cure/treatment. The revolutionary Nobel prize winning CRISPR/Cas9 based genome editing tool to precisely correct a disease causing mutation in somatic or germ cells is the recent one in personalised medicine. This technology has immense applications across life sciences but its clinical use, in human heritable genome editing (HHGE) in particular combined with Assisted Reproductive Technology and Pre-implantation diagnostics should be tread with caution. Scientific evidence for its safety, specificity, efficacy; the consequences of potential off-targets; and more insights into human embryogenesis are essential for its clinical translation. In this paper, we address these issues and highlight the rare group of prospective parents with a SGD where HHGE is the only option to have a healthy biological (genetically related) child. A brief note on the current limitations and the accompanying ethical issues of this technology for clinical use is also added.

Keywords: Human heritable genome editing; Clinical use; Single gene disorders; Healthy biological child; CRISPR edited babies; CRISPR mediated off-targets

Introduction

Genetic variations are the changes in the DNA sequences present in the genome of an organism. These changes may occur naturally due to error in replication of the genetic material during cell division or they may be induced by environmental agents or experimentally; and such changes

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may be present in somatic (non-reproductive) and/or germ cells (sperms and eggs). Unlike changes in somatic cells, those preset in the germ cells are heritable and have been the driving force of human evolution. These DNA sequence variations can range from a single nucleotide base change (G/A/C/T) distributed throughout the protein coding and non-coding regions of the genome to loss or gain of a whole chromosome.

As we understand today, a substantial portion of single base changes have no effect on the regulation or functioning of the genes harboring them or in their vicinity. However, in some instances, a single variation in the protein coding region in a gene may have a detrimental effect on the gene-product and is then termed as a mutation. Such a mutation may lead to a disease and such diseases are variously termed as single gene/monogenic/Mendelian disorders. These generally occur in families with a clear mode of inheritance and therefore also referred to as familial inherited diseases. These contribute to ~6-8 per cent of all human genetic diseases.

On the other hand, variations in sequences in many genes (oligogenic or polygenic) along with the poorly tractable non-genetic/environmental factors can result in common complex diseases, which are mostly sporadic in occurrence and comprise the majority (~60 per cent) of genetic disease burden. Identifying such variations/mutations leading to disease phenotypes is the overarching goal of discovery genomics researchers (Ku et al., 2010). With the help of conventional recombinant DNA and contemporary next-generation sequencing technologies we have come a long way in understanding the molecular basis of a large number of such inherited diseases (https://www.omim.org/). Consequently, molecular genetic diagnosis of such diseases with notable implications for their prediction and prevention in a family or population are common place.

It is thus clear that knowledge of the genetic defect underlying a disease phenotype is a prerequisite to its prevention. Molecular diagnostics for several such common single gene disorders (SGDs) are routinely offered in hospitals or diagnostic centers which enable families or prospective parents with family history of a SGD to know their mutation carrier status. Prenatal diagnostic testing (PNDT) is also offered to such families to help them take informed decision on Medical Termination of Pregnancy (MTP) in the event of a fetus being affected or is a carrier.

With notable advances in Assisted Reproductive Technology (ART), it is however now possible for prospective parents from families with SGDs to avail *in-vitro* fertilisation (IVF) option followed by screening of embryos to identify their normal or affected or mutation carrier status, prior to implantation in a prospective mother (Fig. 1) (thus eliminating the PNDT and MTP processes). This is termed as pre-implantation diagnosis (PID) or pre-implantation genetic screening (PGS) (Soini et al., 2006). However, in a few situations, due to the genetic makeup of the parents and/or infertility, such options are either not available or have a low success of having healthy embryos for implantation. In the absence of effective treatment or cure for most of these SGDs, alternatives for prevention and if not, the best possible way of treatment are highly desirable.

Gene therapy is one of the options available today for treatment/cure of a few SGDs. This therapy includes addition or inhibition of a gene product in the cells of the affected tissue where a mutation either results in a loss of function or over-expression of a functional product leading to the disease. However, there are major technical limitations in this approach (Gonçalves & Paiva, 2017). Furthermore, all gene therapies target the somatic cells of pathologic relevance and thus only the patient is benefitted but the disease can still be passed on to the next generation through the mutation bearing germ cells.

Keeping in mind this limitation in gene therapy, a sophisticated technology to edit or correct a mutation in the cells of an embryo and termed as Human Heritable Genome Editing (HHGE) has attracted considerable attention of clinicians, researchers and affected families in the last four to five years. With the help of advanced genome editing technologies such as Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)/Cas9 the genetic defect in the germ cells (currently possible in sperms only) or in the single cell embryo may be experimentally edited to a normal (original or wild type) sequence, desired edit confirmed by PID prior to implantation in the prospective mother (Fig. 1) and thus preventing the disease occurrence in the respective family (Turocy *et al.*, 2021).

This paper attempts to present the inheritance patterns of SGDs and the genetic (allelic) makeup of the parents for a specific gene, wherein HHGE is the only possible way to have a healthy biological (genetically related)

child. Equal emphasis is given to the current limitations of this technology and the accompanying ethical issues.

Human Genetic Diseases – Predictive Testing and Prevention Strategies

As mentioned in the preceding paragraph, ~60 per cent of all genetic diseases are common complex traits. These include for example Type-2 Diabetes, Cardiovascular Diseases, Rheumatoid Arthritis, Hypertension etc. and gene-environment interactions have been implicated in their etiology. Despite intense genomics research over the last two decades, identification of genetic determinants for such diseases, and their use for prediction and prevention possibilities remain distant and are not covered in this article. On the other hand, a SGD is caused by a mutation in one gene which may be present on an autosome or on the X-chromosome. Accordingly, SGD follows a typical Mendelian mode of inheritance which may be autosomal dominant or autosomal recessive; or X-linked dominant or X-linked recessive as briefly described below. Permutations and combinations of normal alleles and disease causing alleles may occur in different families and the probability of having affected children in such situations/families can vary considerably (Fig. 2, Table 1).

Autosomal dominant: is generally a late onset condition where one disease causing mutation in a gene on an autosome is sufficient for disease manifestation as these are largely gain of function changes. Examples include common human diseases like Huntington disease, Myotonic dystrophy type 1, Neurofibromatosis type 1, Polycystic kidney disease 1 and 2 and Hypercholesterolemia type B etc. (Fig. 2A). In very rare situations, both parents could be affected with one or two disease causing alleles (Fig. 2A i-iii). In a few other but less rare situations, both the alleles in one parent could be carrying the disease causing mutation and all children born would be affected (Fig. 2A iv-v).

Autosomal recessive: Conversely, two disease/mutated alleles of a gene are required for disease manifestation in the case of autosomal recessive group of disorders, which are mostly early onset. The mutation may be at the same location in both the alleles or in some instances, there may be two different mutations in the same gene (compound heterozygote) leading to

Table 1: Shows parental health and genotype status for different disease inheritance models & the probability of having affected progeny

S.No.	Mode of disease inheritance & parental status	Probability of having affected progeny
A.	**Autosomal dominant** **'a' – normal & 'A' - disease allele**	
i)	Both parents homozygous (AA) and affected	100%
ii)	Either parent homozygous (AA) and other parent heterozygous (Aa) but both affected	100%
		100%
iii)	Either parent homozygous (AA) and affected and other parent normal (aa)	100%
		100%
iv)	Both parents heterozygous (Aa) and affected	75%
v)	Either parent heterozygous (Aa) and affected and other parent normal (aa)	50%
		50%
B.	**Autosomal recessive** **'A' – normal & 'a' - disease allele**	
i)	Both parents homozygous/compound heterozygous (aa) and affected	100%
ii)	Either parent homozygous/compound heterozygous (aa) and affected and other parent heterozygous (Aa) carrier*	50%
		50%
iii)	Both parents heterozygous (Aa) and carrier	25%

** carrier – with one disease allele*

Table 1 continued...

Table 1 continued...

S.No.	Mode of disease inheritance & parental status	Probability of having affected progeny	
		Son	Daughter
C.	**X-linked dominant** **'x'– normal & 'X'- disease allele**		
i)	Father affected (XY) and mother homozygous (XX) affected	100%	100%
ii)	Father affected (XY) and mother heterozygous (Xx) affected	50%	100%
iii)	Father affected (XY) and mother normal (xx)	0%	100%
iv)	Father normal (xY) and mother homozygous (XX) affected	100%	100%
v)	Father normal (xY) and mother heterozygous (Xx) affected	50%	50%
D.	**X-linked recessive** **'X'- normal & 'x'– disease allele**		
i)	Father affected (xY) and mother homozygous (xx) affected	100%	100%
ii)	Father affected (xY) and mother carrier (Xx)	50%	50%
iii)	Father normal (XY) and mother homozygous (xx) affected	100%	0%
iv)	Father normal (XY) and mother carrier (Xx)	50%	0%

Source: Authors' own compliation.

the disease phenotype. Examples of such disorders include Cystic fibrosis, Sickle-cell anemia, Phenylketonuria, Thalassemia and Albinism type II etc. (Fig. 2B).

Individuals with only one mutated allele in this category are unaffected and referred to as carriers. These mutations generally result in a loss of function where the gene product is either completely absent or insufficient leading to the disease phenotype. Due to a genetic phenomenon of heterozygous advantage, some populations have relatively higher presence of carrier individuals resulting in a higher number of affected individuals

(example - Sickle-cell anemia). Also, in populations where there is high consanguinity, such recessive diseases are highly prevalent.

X-linked dominant: One mutant allele of a gene present on the X-chromosome is sufficient to cause the disease. These include common diseases like Hypophosphatemic rickets, Rett's syndrome, Fragile X syndrome etc. (Fig. 2C). Since females have two X-chromosomes, the affected females may be heterozygous and, in a few cases, homozygous, but all affected males (XY) will be hemizygous with a single X-chromosome. X-linked dominant disorders are common among the females (heterozygous) since affected males with a single X chromosome are mostly embryonic lethal.

X-linked recessive: Both the alleles of a gene with mutations present on the two X-chromosomes are responsible for the disease phenotype in females; and all males with one mutated allele will be affected since they have only one X-chromosome (Fig. 2D). These include common human diseases like Hemophilia A, Duchenne muscular dystrophy and Glucose 6-phosphate dehydrogenase deficiency etc. In some instances, females with only one mutated allele (carrier females) may manifest the disease phenotype due to a random X-inactivation phenomenon. (Since the females have two X-chromosomes but males have only one, to balance the dosage of gene product, one of the X-chromosomes in females is randomly silenced/ inactivated. Therefore, in some carrier females, normal allele might get suppressed and the mutant allele is expressed resulting in disease).

All these disease conditions although individually rare, together they impact millions of individuals and their families. In almost all the four above mentioned SGD categories (except genetic conditions shown at Fig. 2A i-v; B i; C i & D i), in which molecular diagnostic tests can be performed at the prenatal stage or with IVF mediated ARTs and PID, available at a few hospitals and IVF centers, affected or carrier parents have a fair chance of having a healthy biological child. But a very small proportion of prospective parents have no chance of having a healthy genetically related child due to either two mutant copies of an autosomal dominant disease gene being present in one affected parent; or both parents are affected and homozygous for the autosomal recessive disease alleles (Fig. 2A i-v & B i).

The only conventional options available to them would be adoption or ART using normal gametes (sperms or eggs) from disease allele free donors. However, in the case of humans, unlike procreation in animals, unquantifiable emotional or anxiety quotient to have a healthy biological offspring outweighs these alternatives. In these cases, HHGE, the most recent, powerful, ambitious though controversial and at this juncture, not fully ready and therefore unethical seems to be the only option to fulfil this desire. The science, risks and benefits, limitations and ethics of this technology are presented briefly below.

Current Technological Limitations

Significant progress is being made in the domain of genome editing on the whole and HHGE for clinical use to fulfil the goals of personalized medicine. Substantial portion of this work is aimed at improving the editing technology *per se* being fully aware of its current shortcomings. Recently, catalytically inactive Cas9 fused with programmable deaminases provides further opportunities for gene editing. While these efforts are on, it would be appropriate to present a broad view of the major concerns of this technology and its 'unreadiness' for clinical use, in the context of this article. Genome editing with CRISPR or any of the other similar technologies is not 100 per cent foolproof, on-target efficiency and off-target edits being the primary concerns. Precision with which the desired edit can be made is highly desirable.

Equally if not more desirable is to ensure that there are no additional changes brought in the genome due to the methodological steps themselves. Following Cas9 cleavage, non-homologous end joining (NHEJ) is preferred over homology-directed repair (HDR) whenever a DNA repair mechanism tends to repair any double stranded DNA damage in the cell. This however poses a challenge when we aim to perform a mutation repair in one or more of the cells from early embryos, which are diploid and have two copies of the genes/alleles – one each from each parent. In most instances, indels will be generated at the target site, either at one allele or both the alleles based on the Cas9 cutting efficiency determined by sgRNA binding, amount and duration of Cas9 expression in the cell, chromatin structure and cell cycle stage.

Even though, HDR has been successful in one allele, the repaired allele can be still targeted if silent mutation in PAM sites is not introduced due to continuous Cas9 activity. In the other event, the second allele is still prone for indel generation and only in a very rare instance, we may get the desired mutation in only one allele (heterozygous) in a cell. For correcting both copies of the genes, two independent events have to be followed which is extremely rare. These limitations can be overcome by using small compounds that either block NHEJ pathway or enhance HDR in the cell, using Cas9 protein over plasmids to limit the duration of its availability in a cell, using Cas9 nickase to generate single stranded DNA break and performing cell cycle synchronisation before transfection.

Another concern of CRISPR/Cas9 are the off-targets, which are mainly dependent on sgRNA binding (with some mismatch) at unintended genomic locations. This can disrupt other genes by generating indels and even in some instances result in chromosomal rearrangements and in other cases, disrupt tumor suppressor genes leading to serious pathologies like cancer. To overcome potential off-targets, use of engineered Cas9 protein with lower error rates and nickase Cas9 which rely on single stranded DNA cut are recommended (Uddin et al., 2020).

Embryo mosaicism that is embryonic cells from one embryo having different genetic make up is another major limitation of using CRISPR/Cas9 or in fact any other genome editing technologies aimed at germline genome editing. Editing is preferably done at a single cell zygote stage, but with multiple zygotes obtained from the IVF cycle at one time. However, unchecked cutting efficiency of Cas9 in cells following cell division or Cas9 protein translation delay can lead to a mixture of cells with different genetic makeup at a later stage.

Currently a few alternatives such as performing genome editing in early pronuclear zygotes or spermatogonial cells (oogonial cells currently not amenable for study) are being used to avoid mosaicism. However, there are very limited data available on the DNA repair mechanism in human embryos with most studies being performed on mouse and other model organisms. Besides, there are also inter-species differences in growth and development of an embryo to grapple with. With these notable concerns of potential off-targets of CRISPR/Cas9 editing tool, the possibility of a

successful embryo genome editing seems distant (Mehravar *et al*., 2019).

It is imperative to mention the implications of such undesirable off-target edits in an embryo genome. Notable advances have been made in human genome analysis over the last two decades. It is known that <2 per cent of the genome codes for proteins and uncovering the precise function regulatory or otherwise of the remaining presumably non-coding regions is a continuing biomedical challenge. Common complex diseases are caused by variations in many genes together with an environmental component and these are generally late onset disorders as mentioned previously.

Furthermore, the genes/variants conferring disease risk singly or through gene-gene interactions etc. are poorly understood. Given this, short or long term effect(s) of off-target changes generated anywhere in the genome by CRISPR/Cas9 or any other editing tool, would be extremely hard to assess. Thus, we have no exhaustive understanding of the genome architecture, direct and cross talks between a few or more of the genome-wide variations determining the complex systems biology and through an individual's life span.

Furthermore, a desired edit may be achieved which can be confirmed by very speedy and reliable techniques such as PCR-Sanger sequencing. However, for determining other off-target changes which could be anywhere in the genome, it would be essential to use a battery of techniques including single cell whole genome sequencing, array CGH for copy number variations etc. Distinguishing the editing mediated unintended variations from *de novo* variations which can occur in a genome (approximately each individual has an average of 70 *de novo* single base variants and 6 *de novo* indels) is yet another challenge. Taken together, with all information on the variants but with no insights into their actual role in organismal biology neither short term nor long term effects of off-target changes can be visualised and predicted. With such constraints are we ready to play God? What would be the ethical, legal and social considerations that we would have to address under these circumstances?

Ethical considerations

It is evident from science and technology, clinical use or medicine and individual perspective of HGGE detailed above - that the ultimate step

for prevention and/or cure of an inherited SGD seems to be coming along through desired genomic sequence editing. Clinical use of this tool may be necessary only to enable a very small proportion of prospective parents, with rare genetic constitutions implicated in (serious) SGDs, who have no other contemporary interventions to seek, to have a healthy biological progeny if they so desire; the specificity, safety and efficacy of the desired gene edit remains to be assessed in human embryos; the short term and long term consequences of small or big undesired, off-target changes in the genome of the edited embryo are too far from being addressed; and therefore, this powerful technology is neither tested sufficiently nor ready for clinical use at this point in time. In strong contrast to genetically modified crops which involves use of various methods of man-made selection, hybridisation and mutation introduction for crop improvement, genetic engineering in human embryos has notable bioethical concerns including its potential for eugenics.

The power of the tool to design human babies with improved traits, to prevent infectious disease like HIV, and many more under the realm of designer babies, literally to tailor the next generations cannot be ignored. Social inequality considering the cost and access to such technologies, anxiety and emotional burden of parents and also genome edited babies as they grow up and many more ethical issues may emerge (Halpern *et al.,* 2019).

Given these, any attempt to perform HGGE to produce 'edited healthy babies' raises serious ethical issues, with global implications for the human race itself. If and when 'unambiguously ready', the initial uses of HGGE should be restricted only to the small group of prospective parents with a serious SGD and with no options except HGGE to have a healthy biological child.

Though the ultimate goal of medicine using all advanced technologies may be to ensure a genetic disease free society/population, we need to tread with caution. Finally, though the primary and periodic assessment of this emerging technology and permitting its clinical use has to be each country's utmost responsibility and to be implemented through its regulatory bodies and policy makers, the need for an international oversight mechanism and global engagement to ensure 'appropriate clinical use of HHGE only when ready with scientific evidence' is inevitable.

At this point , in our opinion, the status of HHGE, is best described as *"You're building an expensive bridge to a remote island before we know if we are ready to use it"* **(A**nonymous expert comment in: Perspectives, The CRISPR Journal, 3 (5) pg. 333, 2020).

Endnotes

1. Editing of gametes (sperms and eggs) to correct a disease causing mutation in the category of prospective parents with no other options to have a biological healthy child; editing of gametes/germ cells/embryos for trait improvement in humans; and for likely prevention of infectious diseases etc. are not dealt with in this paper.
2. The online link for the webinar where the broad contents of this article were presented is also available at https://www.youtube.com/watch?v=HLXQITDGZG8, Webinar on Nobel for CRISPR organised by Research and Information System for Developing Countries.
3. An announcement of CRISPR babies made in the second International summit on human genome editing in 2018 shook the scientific community. This mirrored the serious reservations for the societal acceptance of HHGE in the absence of scientific evidence of its safety. This led to the appointment of the 'International commission on the clinical use of human germline genome editing' by the U.S. National Academy of Medicines, the National Academy of Sciences, and the U.K.'s Royal Society in 2019 with members from 10 countries. The report of the commission published in September 2020 is available at https://www.nap.edu/catalog/25665. The Academies will revisit the Commission's analysis, conclusions and recommendations in the third International human genome editing summit in 2021. World Health Organisation also has recently brought out a report on "Genome Editing: A Framework For Governance" (https://www.who.int/publications/i/item/9789240030060).
4. BKT served as a member in the above mentioned International commission. In this article, an attempt has been made to summarise the salient points of the HHGE report. The authors are geneticists/stem cell biology researchers.

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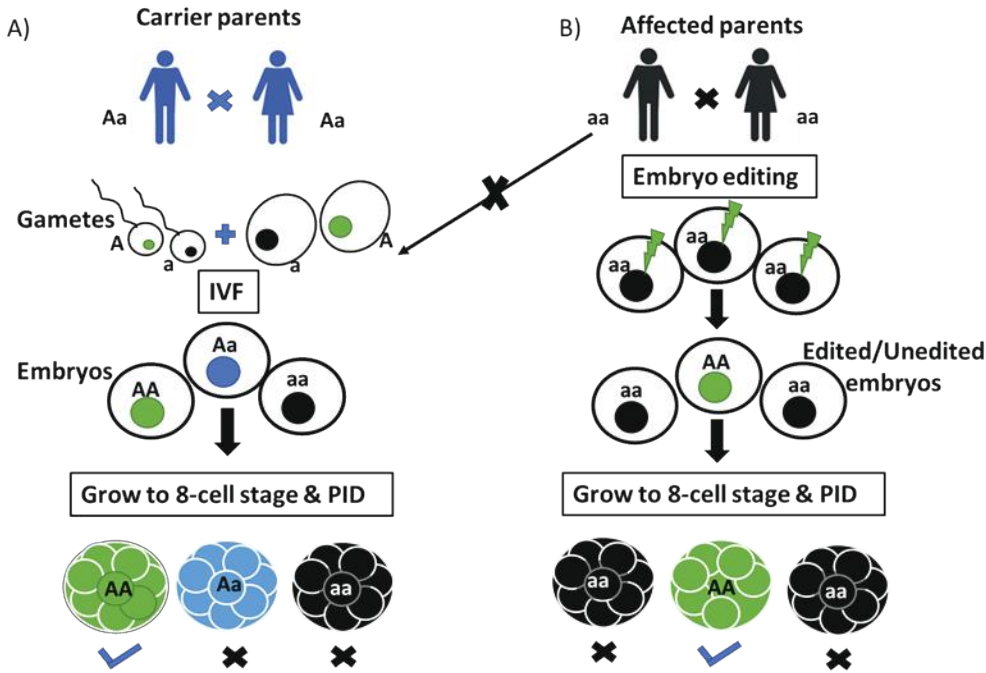
Figure 1: A) the conventional *in vitro* fertilisation (IVF) followed by pre-implantation diagnostics (PID) for detection of healthy (AA)/ carrier (Aa)/affected (aa) embryos; & B) IVF followed by embryo editing and detection of successfully edited embryo(s) by PID, in different families, with an autosomal recessive disorder as an example. (Please note: Affected parents at (B) have zero chance of having a healthy progeny without HHGE intervention.).

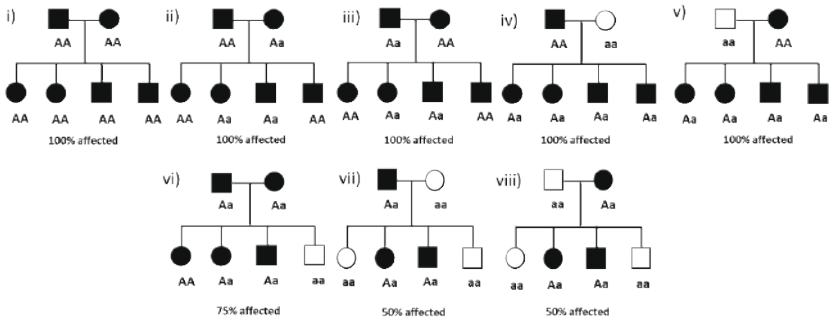


Source: Authors' own compilation.

Figure 2: Hypothetical pedigrees with all the possible allelic combinations for a gene on - (A,B) an autosome; & (C,D) X-chromosome, which may occur for a single gene disorder; & the probability of having affected progeny in the respective situations.

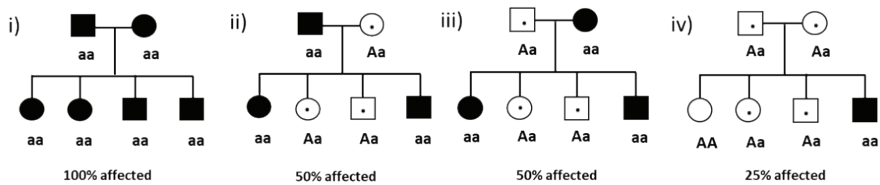
■● – affected; ⊙ - carrier & □○ - normal

A) Autosomal dominant



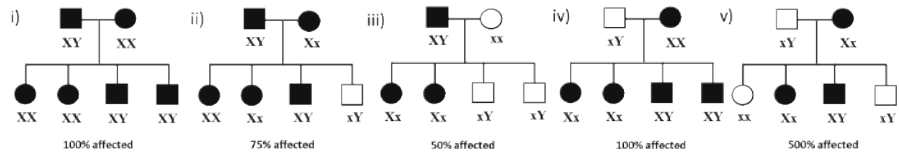
Note: **'a' – normal & 'A' - disease allele; i-v – 100% progeny affected; vi – 75% affected; & vii-viii – 50% affected**

B) Autosomal recessive



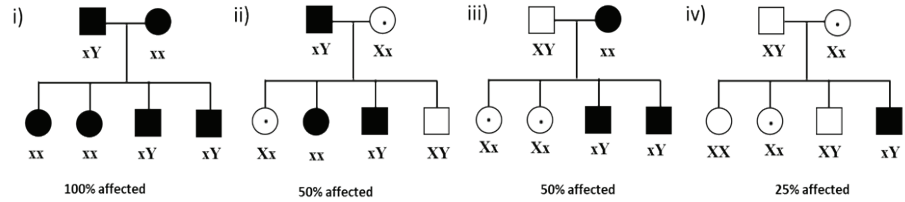
Note: **'A' – normal & 'a' - disease allele; i – 100% progeny affected; ii-iii – 50% affected; & iv – 25% affected**

C) X-linked dominant



***Note:*'x' – normal & 'X' - disease allele; i & iv – 100% progeny affected; ii – 75% affected; & iii & v – 50% affected**

D) X-linked recessive



Note: **'X' – normal & 'x' - disease allele; i – 100% progeny affected; ii-iii – 50% affected & iv – 25% affected**

Source: Authors' own compilation.

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Model Legislation and the Transnational Governance of Human Heritable Gene Editing

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Abstract: Traditionally, governance of technology is left primarily to nation-states. Emerging technology often challenges this governance approach, mainly when technology circulates across national boundaries. This paper explores the potential of model legislation to integrate the traditional approach to make technology governance more robust internationally. Model legislation comprises various strategies aimed at developing regulatory instruments that can form the basis of regulation at the national level. Using advances in technology to modify the human germline, the paper analyses transnational challenges governing this technology and argues that some of the lessons learned by studying how UNCITRAL, a United Nations body, develops model legislation can be successfully applied to the governance of human germline gene editing. The paper advocates for developing comprehensive model legislation and legislative guides around human gene editing, which lawmakers and regulators at the national level can use to model legal reform.

Keywords: gene editing; CRISPR; transnational governance; model legislation; UNCITRAL; governance of technology

Introduction

In this paper, I explore the potential of using an approach to regulating emerging technology with a transnational impact rarely used in governing innovation: model legislation. Model legislation comprises a variety of strategies aimed at developing regulatory instruments that can form the basis of regulation at the national level. While geared primarily to regulating technology at the national level, model legislation offers benefits in terms of transnational governance, a normative system that operates across and beyond the nation-state (Djelic and Sahlin-Andersson, 2006).

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Model legislation, I argue, helps address some of the regulatory challenges that emerging technology presents. A technology may present novel risks; its impact may be unknown or difficult to predict; it may push the ethical boundaries of what is generally agreed as acceptable; it may call for a regulatory framework based on new principles. Regulatory issues can be roughly divided into two camps: "if" and "how" issues. "If" issues raise the question of whether an emerging technology should be allowed to develop further. Classical "if" issues stem from assessing risks and benefits of a technology or unsettled ethical issues. "How" issues assume the further development of emerging technology and focus on how that technology should be regulated. "How" questions concern the adequacy of the existing regulatory framework, the need for modest adaptation, more comprehensive reform, or an entirely new framework.

In a globalised world, emerging technology typically presents itself with transnational governance challenges. "If" and "how" questions are inextricably linked to how that technology is regulated in other jurisdictions. Technology may be developed in a particular place (a university or a company) and be controlled by local rules. However, any successful technology will soon spread in other jurisdictions. Even the assumption I just made—technology is produced in a particular place and time—is problematic because rarely is technology the result of a developer or a team of developers operating in a single location. Ideas, data and information, knowledge, experiments, and pilot programs result from groups of people acting in different parts of the world. The current production model of technology and its global circulation challenge the traditional approach to governance, which relies almost exclusively on national laws. Using human germline gene editing—technology that human modifies germline cells—as a case study, I delve into the possibilities that model legislation offers to make transnational governance of emerging technology more robust and effective.

After discussing the transnational governance challenges of human germline gene editing, I discuss what model legislation is and its use in transnational governance. My analysis draws from the successful experience of UNCITRAL, a United Nations body, to coordinate national frameworks in the areas of commercial law. I explain how UNCITRAL operates and the model legislation has produced. I then apply the lessons

learned from the UNCITRAL experience to transnational governance of human germline gene editing to illustrate the potential of this approach in regulating innovation.

The model legislation strategy, I believe, facilitates the management of "how" challenges domestically, particularly for countries with weak international science policy expertise. At the same time, the process of developing model legislation offers the forum to debate "if" questions, eventually leading to coordination and possibly convergence of national legal frameworks towards few, thus towards few viable policy frameworks. Using model legislation to construct coherent domestic legal frameworks facilitates the responsible circulation of technology globally without sacrificing national variation of policies.

Transnational Challenges of Human Germline Gene Editing

The advent of CRISPR and the resulting acceleration in humans' ability to modify genetic codes is one of such emerging technologies (Davies, 2020). This technology, importance of which has been recognised by the Nobel Prize committee's decision to award the 2020 Nobel Prize in Chemistry to Emmanuelle Charpentier and Jennifer Doudna, is now ubiquitous as it is used in labs around the world.

While most of its uses are hardly problematic, some are (Baylis, 2019). The editing of human germline cells is one of such uses. The ability to edit germline cells means that humans deliberately produce changes to the human genome that can be passed to future generations. The potential for treating inherited genetic conditions for which, at the moment, there is no treatment and very little ability to intervene, besides embryo screening and selection after fertilisation, is compelling. On the other hand, germline editing involves interventions on embryos and germ cells (sperm and oocytes), ethical acceptability of which is unsettled and certainly not uniform across countries, cultures, and societies.

This diversity of ethical perspectives is reflected in legislation at the national level. As my research shows, the regulation of research and clinical interventions on the germline varies significantly from country to country (Andrea Boggio et al., 2019). Research with embryos is prohibited

in some countries. Most prohibit clinical research involving the ending of the germline. If ever proven safe and efficacious, the normative landscape of the clinical use of this technology also varies significantly around the world. This approach to regulating human germline modifications, and the technology used to implement these modifications, looks more like a normative kaleidoscope than a single, unified picture. The transnational governance implications of these gaps are significant. Basic research on germline gene modifications could be lawfully conducted in Country A; clinical research in a Country B, and the technology could be offered to patients in Country C, assuming the regulators approve for marketing or no government preapproval is needed.

Aspects of this scenario became a reality in 2018 when the world became aware of the birth of the female fraternal twins known as Lulu and Nana (Greely, 2021). The newborns carry altered copies of the C-C motif chemokine receptor 5 (CCR5) gene. The alterations were implemented using CRISPR-Cas9–based genome editing by a biophysicist and his team at the Southern University of Science and Technology in Shenzhen, China (I refer to him as HJ to avoid amplifying his name giving him further notoriety). Within a matter of hours since the birth of the twin girls come to the surface, a prompt and virtually universal "international outcry" spread among leading scientific publications and news outlets (Cyranoski and Ledford, 2018). The CRISPR pioneer and late Nobel Prize winner Jennifer Doudna indicated that she was "horrified by the news (Yong, 2018). Hank Greely stated that the experiment was "criminally reckless" and called the work "grossly premature and deeply unethical" (Greely, 2021:147).

While not opposed in principle to heritable germline editing, I believe that international outcry was warranted ("Germline gene-editing research needs rules," 2019). This episode encapsulates the transnational shortcomings of current approaches to regulating this technology: in 2018, and this holds true today, there was no international consensus that experimenting with gene editing on humans was acceptable. While many, but not all, consider basic research involving embryo manipulation or creation to be acceptable, nobody has openly endorsed transferring embryos resulting from editing cells in patients with the goal of reproduction. Indeed, there is no global consensus on the acceptability of the clinical use of germline gene editing, and perhaps there will never be. Indeed, though, the birth of Lulu and Nana

violated the principle that disruptive and controversial uses of technology require some degree of global greenlighting. Quite simply, the experiment had been carried out outside the accepted norms of responsible science and in breach of the Hippocratic commitment not to harm.

A critical aspect of the story that is HJ's action cannot be simply labelled as the exploits of a bad apple. While some cast his figure as a "rogue scientist," the factual record shows that his plans had been known and partially enable by what Ryan Ferrell, a public relations specialist hired by HJ, named HJ's "circle of trust" (Cohen, 2019). According to reporting by Jon Cohen (Cohen, 2019:431):

> *That circle included leading scientists—among them a Nobel laureate—in China and the United States, business executives, an entrepreneur connected to venture capitalists, authors of the NASEM report, a controversial US IVF specialist who discussed opening a gene-editing clinic with [HJ], and at least one Chinese politician […] Some people sharply criticised [HJ] when he brought them into the circle; others appear to have welcomed his plans or did nothing.*

Some aspects of how the "circle of trust" operated are essential for analysing transnational governance of emerging technologies presented in this paper. Reportedly, some individuals within the "circle of trust" wanted to do more than just try to dissuade him. They would have liked to stop him but did not know how to do it and ended up not even attempting. To their defences, they were not familiar with legal or institutional pathways to stop HJ from carrying out the experiments in China or internationally. Chinese law itself was not crystal clear about the legality of the experiments. In fact, a court held HJ criminally liable but not for breaching a law prohibiting the experiments. The conviction was based on fraud (Greely, 2019:166). This means that, even if they had sought legal advice from an expert on Chinese law, a member of the "circle of trust" would have not concluded that the experiments were not *per se* illegal.

Challenges in Navigating Regulatory Frameworks

The last statement raises an important point. A scientist trying to navigate the lawfulness of HJ's actions by doing her own legal research would

have likely failed to come to the firm conclusion that HJ's activities were *prima facie* lawful. The criminal code was only recently amended to expressly prohibit the implantation of genetically edited or cloned human embryos into human or animal bodies. Difficulties in deciphering the lawfulness of heritable human genome modifications are not exclusive to the Chinese legal system. A comprehensive analysis of the regulation of this technology in eighteen legal systems has revealed that, for the most part, regulatory frameworks are inconsistent and legal provisions present gaps, contradictions, and uncertainties (Boggio et al., 2020:157). It is also interesting to note that, as one of the coordinators of that analysis, I observed that the legal experts who contributed often could not answer some of the straightforward questions about how heritable human genome editing was regulated. As I noted elsewhere, "one can guess how perplexed scientists must be" if they attempted to conduct their own research into laws and regulations, particularly of a foreign country (Boggio et al., 2021).

The problem is further compounded when a person from outside that legal system tries to grasp how heritable genome editing is regulated. To date, no country has enacted comprehensive legislation addressing the specific issues raised by the advent of gene editing techniques. Comprehensive legislation would be a regulatory framework that regulates *all* segments of the research-to-applications pipeline, from bench to bedside (basic research on gametes and embryos, clinical trials that enrol human participants for heritable editing, and clinical applications of germline editing). Instead, countries have approached the problem by regulating individual segments of this pipeline. This means a coherent understanding of how the research-to-applications pipeline is regulated can only be the product of patching together provisions from different legal sources. This highly sophisticated process requires training in that legal system, particularly considering that some countries do not even have proper regulation for all segments.

Another problem is that key terms appearing in laws and policy statements are "vague and poorly defined, rendering their application challenging and decision making subjective and arbitrary" (Kleiderman et al., 2019). Further, countries may make inconsistent use of definitions. This is the case of the "human embryo," which is defined inconsistently across countries: some definitions are based on what the entity is at a particular point in time (e.g., Australia, Canada, Singapore), while some on

its capacity to develop into an individual or a human being (e.g., Belgium, Japan, Germany, and the Netherlands). Some do not even bother defining it (e.g., Israel, Italy, and Sweden)(Isasi et al., 2016).

The result is a fragmented legal landscape that is hard to navigate domestically and even harder to coordinate with other legal systems. This is made even more problematic because most legal frameworks rely on inherited rules (Stokes 2012), that is, rules adopted before the advent of CRISPR. Except for Japan and now China, most legal instruments were drafted, debated, and enacted before 2010 with significant legislative activity in the late 1990s/early 2000s, when gene editing was not on the horizon. Only some countries (e.g., France, Israel, Singapore, South Korea, Sweden, the Netherlands, and the United Kingdom) have undertaken formal policy discussions on germline gene editing in the past five years or so. The result is that statutory language that neglects gene editing. In fact, most laws neither prohibit nor permit germline genome modifications expressly.

This raises an interesting tension at the level of "if" questions in these jurisdictions: their regulatory framework rejects basic research and admits applications. Typically, the objection to basic research on germline modifications is fundamental, having to do with embryos' moral status. Yet, because of advancements in other countries, made possible by a more permissible regulatory framework, technology is seen as valuable if beneficial to the embryo. It seems hypocritical to accept from the backdoor (as an application) a technology when the main door (basic research) remains shut on moral grounds. Clearly, no heritable gene editing can ever become a licensed practice without creating and destroying embryos and experiments on willing research subjects.

Calls for Strengthening Global Governance

In the aftermath of the birth of Luna and Nana, international efforts to develop a more robust international regulation of heritable human genome editing gained momentum. Two committees of experts were tasked with improving global governance mechanisms of heritable gene editing. These are WHO's Expert Advisory Committee on Developing Global Standards for Governance and Oversight of Human Genome Editing (WHO Committee) and the International Commission on the Clinical Use of Human Germline

Genome Editing convened by the US National Academy of Medicine, the US National Academy of Sciences, and the Royal Society of the United Kingdom (International Commission).

The International Commission issued a report in September 2020 focusing primarily on scientific understanding, future clinical uses of heritable gene editing, and the necessary elements of any translational pathway. Its recommendations touch upon the need to develop regulatory frameworks with standards and procedures that can enable regulatory agencies to properly oversee the use of this technology. It also proposes an International Scientific Advisory Panel tasked with assessing scientific evidence of sage and efficacy of genome editing and the associated assisted reproductive technologies. Regarding the critical question of this paper (global governance of emerging technologies), the International Commission adopts a mixed approach, combining two governance levels—the global with the local. The global governance level relies upon universally agreeable principles and the appointment of an expert body tasked with assessing scientific evidence. The choice of whether and how to deploy the technology is a local one, made at the domestic level in consultation with society and formalised in rules and regulations under the authority of national regulatory agencies.

The WHO Committee published a Draft Framework in January 2020 (WHO Advisory Committee on Developing Global Standards for Governance and Oversight of Human Genome Editing, 2020). This document features a more prominent role for transnational governance, which is defined as "a web of separate initiatives" complementing ethical principles that are universally agreed-upon with the contribution of national lawmakers and regulators to facilitate coordination and promote consistency across national boundaries. While recognising the irreducible core of national laws and regulations, the Draft Framework espouses the idea that the path forward in global governance is the "coordination between nations" (WHO Advisory Committee on Developing Global Standards for Governance and Oversight of Human Genome Editing, 2020:3) with organisations such as WHO or UNESCO facilitating the process. It is also important to remember that the WHO Committee also established the Human Genome Editing Registry, a central database that collects clinical trials information using human genome editing technologies.

The policy recommendations of these two bodies reiterate the essential role that national laws and regulations play in global governance. The greenlighting at the country level of heritable gene editing applications has international ramifications, as evidenced by Luna and Nana's birth. A corollary of this observation, I would argue, is that domestic laws and regulations must adequately address this technology, where "properly" does not necessarily mean prohibiting. Instead, it means that national regulatory frameworks, which comprise regulatory instruments and oversight—are well equipped to govern the technology. They are up-to-date and providing clear guidance as to what is lawful and what is not. The WHO Committee goes a step forward, indicating that there should also be an international effort to coordinate these national regulatory frameworks so that the international community possesses a cohesive picture of how the technology is regulated, in different ways, across the globe.

Using model legislation would advance both objectives: more robust regulatory frameworks at the national level and transnational coordination at the international level. Before developing the argument for using this approach to govern heritable gene editing, I will first outline the model legislation approach by examining how UNCITRAL has accomplished this goal with commercial and trade issues.

Model Legislation Explained

Model legislation is the practice of drafting sample legislation to be used by lawmakers as a template. When sponsored by a government domestically, model legislation typically begins by convening a body of experts, possessing subject matter expertise and experience in legal drafting, to produce a regulatory instrument or set of clauses that lawmakers can subsequently use as the basis for debating and adopting new legislation. In some instances, model legislation is initiated by governments at the international level, bringing together experts from a variety of countries to produce a template that will either serve as the foundation for international lawmaking or domestic regulation. Alternatively, model legislation may be promoted by non-governmental organisations, which take on preparing the template and disseminating it to lawmakers. In these cases, the template will find its way into the political process through advocacy or lobbying.

Model legislation has been used successfully at the international level. The most glaring example is the more than twenty legislative instruments prepared by the United Nations Commission on International Trade Law (UNCITRAL) in international business law (UNCITRAL, 2013). The Commission was established in the 1960s to address the need for global standards and rules to harmonise national and regional regulations in international trade and investment. Its official mandate is "to promote the progressive harmonisation and unification of international trade law" through conventions, model laws, and other instruments that address critical areas of commerce, from dispute resolution to the procurement and sale of goods. It is a subsidiary body of the UN General Assembly (UNGA), with a secretariat based in Vienna, Austria, and a membership comprising sixty United Nations members. Countries are elected by the UNGA by secret ballot to the Commission with a mandate of six years. Elected members must represent a diversity of legal traditions, levels of economic development, and regions. Non-member states can attend sessions and participate in discussions of the Commission and its working groups as observers.

The Commission carries out its work at annual sessions held in alternate years at United Nations Headquarters in New York and the Vienna International Centre in Vienna. The bulk of the work is carried out by Working Groups, which currently are six: Micro, Small, and Medium-sized Enterprises; Arbitration and Conciliation and Dispute Settlement; Investor-State Dispute Settlement Reform; Electronic Commerce; Insolvency Law; and Judicial Sale of Ships.

The Secretariat also plays a valuable working of support for the Working Groups, including:

> *preparation of studies, reports and draft texts on topics that are being considered for possible future inclusion in the work programme; legal research; drafting and revision of working papers and legislative texts on topics already included in the work programme; reporting on Commission and working group meetings; and providing a range of administrative services to UNCITRAL and its working groups (UNCITRAL, 2013:9).*

A vital tool at UNCITRAL's disposal is the ability to engage "outside experts from different legal traditions, conducting ad hoc consultations

with individuals or convening meetings of groups of experts in a particular field, as required" (UNCITRAL, 2013:9). Over the years, these experts have produced drafts of conventions and model legislation.

Model legislation may take different forms: conventions, model laws, legislative guides, and model provisions. Conventions are binding treaties establishing legal obligations uniformly across countries that ratify them. They are international legal instruments in a proper sense and targets hard to achieve as they require a consensus, or at least a vast majority of nations agreeing to the development of binding legal instruments and their normative content (rights and duties). Further hurdles come from the fact that UNGA must adopt conventions and then sign or receive the ratification of a sufficient number of Member states to enter into force.

Model laws are templates of comprehensive legal instruments that countries can enact as national laws. Comprehensive means that they are constructed to provide a single, coherent regulatory framework on a particular policy area. In some instances, a comprehensive template incorporating all issues connecting with a specific question may not be technically feasible or politically desirable. These cases are better served with model provisions, which propose regulatory solutions to a single issue or a small set. Model law and model provisions are prepared by Working Groups, sometimes based on drafts produced by expert committees, and then finalised and adopted by UNCITRAL at its annual session. Because of the international character of UNCITRAL, when model laws are adopted, governments become committed to translating model laws into national legislation. Even if this entails a commitment on the part of governments, model laws are politically more achievable than conventions because of the flexibility in implementation. The provisions in model laws are not directly binding governments, and although often discouraged, adjustments to accommodate local requirements are possible. UNCITRAL's model laws are often accompanied by a "guide to enactment," setting forth background and other explanatory information to assist governments and legislators in using the text (UNCITRAL, 2013:13).

Legislative recommendations are a set of legislative recommendations with an explanatory note detailing the rationale of the recommendations. Their text comprises a series of provisions (conventions) or model provisions

(model act) and possible legislative solutions to specific issues. In some instances, a single set of model solutions is proposed. In other cases, legislative recommendations comprise multiple groups of solutions that adoption depends on policy considerations. Discussions of the advantages and disadvantages of different policy choices are an integral component of these recommendations. These instruments are drafted to assist national lawmakers and regulators in evaluating different approaches and enabling them to choose the most suitable for their context. They are also intended to assess existing laws and regulations and stimulate legal reform or the development of a new framework. Legislative recommendations are pursued when attempting to develop a uniform text that is not likely to succeed. Obstacles to uniformity may be technical or political. Technical barriers have to do with national legal systems' using legislative techniques or approaches that are too disparate to suit a uniform approach. Political obstacles may result from the fact that:

> *states may not yet be ready to agree on a single approach or common rule, there may not be consensus on the need to find a uniform solution to a particular issue, or there may be different levels of consensus on the key issues of a particular subject and how they should be addressed (UNCITRAL, 2013:16).*

Model Legislation for Heritable Gene Editing?

Model legislation is an effective strategy to achieve coordination and enhance transnational governance. While its outputs are not directly applicable to governing heritable gene editing, the UNCITRAL model constitutes an important example of how model legislation can be produced internationally and used to strengthen transnational governance of technology. If properly used, model legislation can facilitate coordination across legal systems and stimulate legal reform at the national level. The result would be an emergent "locally based, globally informed governance," mirroring the vision of Kofler et al. (WHO Advisory Committee on Developing Global Standards for Governance and Oversight of Human Genome Editing, 2020:5) for environmental applications of gene-editing techniques.

Would this approach be beneficial to address some of the governance challenges raised by heritable gene editing? Model legislation is rarely used

in science policy. One of the few examples is the World Health Organisation's initiative on electromagnetic fields protection in 2006 (World Health Organization, 2006). However, I believe that transnational governance of heritable gene editing would benefit from integrating model legislation into the current efforts to govern this technology. In the background is the observation that a global governance framework for heritable gene editing revolving around international law is highly unrealistic. Therefore, efforts to strengthen this level of governance are bound to rely primarily on domestic laws and regulations.

Why is the adoption of binding international legal rules unrealistic? One consideration is historical. To date, we can only count two legal instruments that contain binding legal rules on human genome modification and the scope of application of which goes beyond national boundaries. These instruments are the Oviedo Convention and the EU Regulations on Clinical Trials. The Oviedo Convention is a treaty negotiated at the level of Council of Europe, an international organisation grouping 47 member states that include all 27 EU members and 20 other European countries or closely located (i.e., Russia and Turkey). The EU Regulations on Clinical Trials, which will likely enter into full effect at the end of 2020, are a legal instrument adopted by the EU institutions and thus binding all, but only, 27 EU member states.

Both instruments are regional, and consequently, they are binding only in a handful of countries (respectively 29 and 27). Further, the ratification record of the Oviedo Convention demonstrates that a significant number of members of the Council of Europe have decided not to ratify the Convention. As a result, the governance principle embedded in the Convention does not reflect the consensus of the Council of Europe members, let alone a global consensus. Knowing that the relatively small group of countries (47) that are members of the Council of Europe cannot agree on basic governance principles of genome modification, a global consensus is hardly conceivable. At a minimum, the Council of Europe members that have not ratified the Oviedo Convention would oppose a framework that prohibits genome modification. Conversely, countries supporting restrictions on genetic modifications would be opposed to a permissive framework—a highly divided scenario.

The infrequent adoption of multilateral treaties is another indicator weighting against binding international rules. These treaties are becoming the exception in international lawmaking, as remarked by the growing literature on "treaty fatigue" (Pauwelyn et al., 2014). The record in global health governance is particularly meagre. During its history, WHO has adopted only two binding instruments—the Framework Convention on Tobacco Control in 2003 and the International Health Regulations in 2005. Treaty fatigue is even more prominent in science policy. The international community has tried and ultimately failed to finalise treaties banning human cloning (Tauer, 2004) and regulating genomic technologies and interventions (Butler, 1993). The difficulties of overcoming treaty fatigue can also be observed in current efforts to adopt a pandemic treaty. Although COVID-19 has shown the failures of the existing global governance architecture, the path to bringing together the world community to redesign that architecture is far from been and inscribe them in a binding treaty is somewhat unsteady.

Producing soft law instruments is a more realistic option for WHO and other international bodies. UNESCO has adopted various non-binding declarations, including the 1997 Universal Declaration on the Human Genome and Human Rights, the 2003 International Declaration on Human Genetic Data, the 2005 Universal Declaration on Bioethics and Human Rights, and the 2017 Recommendation on Science and Scientific Researchers. These instruments create some obligations for Member states but are not binding (UNESCO, n.d.), and because of that, their ability to strengthen global or transnational governance is inherently limited. This is problematic in the wake of the unwarranted and egregious clinical use of germline gene editing. Given these policy conditions, model legislation presents three advantages.

First, it can facilitate comprehensive legal reform at the national level. Because model legislation would be broad in scope and present a range of choices involving all aspects of the bench-to-bedside pipeline, it will facilitate the adoption of comprehensive legislation on human genome editing, a roadblock to transnational governance. If more nations adopt comprehensive legislation, the global fragmentation would be reduced because, at least, the regulatory picture at the national level would be more apparent.

Second, if adopted as part of comprehensive reform or even in bits, model legislation can promote standardisation and harmonisation of regulatory approaches. Standardisation would bring definitions and usage of legal terms closer. Harmonisation will bring consistency of legal provisions and legal requirements, substantive and procedural, across legal systems. Standardisation and harmonisation would not erase cross-national variation of legal instruments. In fact, variation is not only inevitable, because it is unlikely that lawmakers throughout the world would converge on the same regulatory approach, but also desirable, considering that heritable human genome editing engages differences in ethical views and values within and across nations that cannot be reconciled and, in my opinion, should not be reconciled. Countries should not be forced to permit embryo manipulation if their lawmaking bodies, acting within the boundaries of the rule of law and reflecting societal values, decide against it. However, while policy flexibility is needed, divergence should be tempered, and convergence towards a limited set of options is desirable. This way, gene editing regulatory frameworks could be more easily navigated. Model legislation could develop a selected number of internationally validated policy models.

Third, being a vehicle for modernisation, model legislation will help solve the lag in human genome editing policies. This is partly the result of legislative inertia, which is understandable given that heritable human genome editing confronts lawmakers with a subject matter that is both technically sophisticated and constantly evolving. Lawmakers and regulators are asked to make sense of scientific advancements that are unstable and disruptive and deliver regulation that mediates demands for innovation with societal anxiety. This is not an easy feat. Legislative inertia is also determined by more significant political problems such as short-termism due to frequent election cycles, partisanship, and ideological divisions or regulators' lack of capacity to assess new technology. External support in the form of model legislation would help bring inertia to an end and an incentive for national policymakers "to engage effectively with the governance of human genome editing," as stated in the WHO Draft Framework (WHO Advisory Committee on Developing Global Standards for Governance and Oversight of Human Genome Editing, 2020:5).

Path Forward

In this paper, I argue for integrating model legislation into current efforts to strengthen the transnational governance of heritable gene editing. To implement this idea, an expert body must be established. The easier path would be to convene it under the auspices of an existing international body, likely WHO or UNESCO. This expert committee should include governmental officials, international inter-governmental organisations, non-governmental organisations, academics, and private sector lawyers representing different geographical regions. Conflict of interests must be closely vetted, and representation by expertise and region must ensure low-income countries' interests. This committee would need a budget, a secretariat, and the means to convene, discuss, and deliberate. Its mission would be exclusively to develop model legislation.

While conventions and model acts bring the highest degree of harmonisation and modernisation, they may not be the desirable instrument that this body would produce. Harmonisation may not politically achievable or even desirable, as discussed earlier in this paper. Instead, this body should focus on delivering detailed analyses of the legal issues at stake and offer a limited number of normative models that could be adopted at the national level. These models would use the same terminology and the same structure, so, if adopted at the national level, readers unfamiliar with that legal system could navigate the legislation as it would look familiar. Once the drafting body has deliberated, national legislative bodies should be free to adopt, amend or disregard the provisions recommended by the drafting committee. The accompanying analyses should discuss the advantages and disadvantages of different policy models to assess the different approaches by national policymakers and regulators to identify the most suitable for their political and social environment. If a state adopts any of the recommendations, this model legislation becomes the state's statutory law under the rules governing lawmaking in that country.

A foreseeable object to this approach is to point out that this is just another committee, and we already have enough of them. This may be true in general terms. We do not need an additional committee. Unless it is useful. My reply is that model legislation has never been attempted around heritable gene editing. Its purported advantages, assuming I have persuaded

you, cannot be discounted. Producing model legislation is an efficient and promising approach to developing a locally based, globally informed system of transnational governance for heritable gene editing. The value of harmonisation and modernisation in avoiding the misuse of technology should not be underestimated.

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Gene Editing – Ethical Pathways to Connect Science & Society

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Abstract: Effective translation of scientific advancement for health benefits needs integration of ethical values which can guide better outcomes and help to connect with the society to reap the fruits of knowledge. As gene editing procedures are evolving with a promise to offer a cure for innumerable diseases, the time is right to put in place a suitable governance framework which integrates the ethical and moral values to enable an appropriate use of the proposed technological advancements. The paper discusses the need to include ethical considerations, improved communications, ensure transparency and accountability, accessibility and affordability, building capacity, collaborations, and defined regulatory processes in order to have a better uptake as well as to build public trust in the technology.

Keywords: gene editing, molecular scissors, governance framework, new technology, integrate ethics, ethical values, build public trust.

Introduction

In the year 2020 The Nobel Prize for Chemistry was awarded to two women scientists for their research work involving development of method for genome editing. This was a huge encouragement for the emerging role that this promising technology may play in improving human health in the near future[1]. The power of CRISPR-Cas9 technology and other similar molecular scissors used for editing the gene may allow scientists to make major strides in tackling serious debilitating diseases which otherwise have no cure. There is a potential to treat more than 10000 monogenic genetic conditions as well as complex polygenic disorders. These technologies offer huge hope, though it's still a long way to go. It is important to start planning for a suitable governance framework that would enable appropriate use of the proposed technological advancements. The ethical and moral considerations must get integrated in this evolving governance framework right from inception.

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This framework would guide the researchers as well as policy makers in the development and implementation of this new technology and thereby help the society to reap the full benefits.

During the last decade, bioethicists and researchers from across the world have debated and have pointed out a number of concerns regarding ethical and societal issues that may arise due to use of gene editing technology (Brokowski and Adli. 2019; Fani et al, 2018). Thus, the time is ripe for India to discuss scientific and ethical concerns, propose a regulatory and governance framework, identify ways of tackling biosafety issues related to the use of the novel technology. On one hand there is need to support basic science research and on the other hand identify and define what would be socially relevant research for betterment of mankind. In view of the large size and population which is multilingual, multicultural, socio economically diverse, having different religious beliefs, enormous efforts are needed to rightfully reach out to the stakeholders and explain about the technology and its pros and cons. Steps have to be initiated to facilitate improved understanding and create opportunity for autonomous decision making based on actual facts rather than false beliefs. A lot of efforts have to go hand in hand to engage, educate, improve dialogue and understanding the societal concerns. Since this is a new technology, that is still evolving but has an untapped enormous potential, all stakeholders need to work together to explore newer avenues to fulfil the promise towards unprecedented improvements in human health.

Somatic and Germline Editing

The capability to make precise changes to the human genome whether somatic or germline raises all kinds of difficult questions about how far we should go ahead with it for it to be used in a manner that is accepted by the society. This is also the time to discuss and understand the basic differences related to the fact that the changes could be heritable in case of germline gene editing and therefore there are some questions whether genome editing be used to avoid genetic diseases or can it be justified for genetics enhancement for serious disorders. It's time to think where does one draw a line about what can or cannot be allowed. Should germline gene editing be allowed for some conditions? What kind of heritable changes can be allowed to be inherited? What can be the long term effects of these

changes and is there a worry related to changing the gene pool? Can they create mosaics? Are there possible effects on the future generations? There is dilemma if the germline gene editing would qualify as a boon or bane for mankind (Krishan *et al*, 2018). Somatic cell gene editing may require very similar treatment to other research since the changes are not a heritable and will not go to the next generation. It has a therapeutic potential and may eradicate disease promising a better life. However, there is need for abundant caution since in the present state of our knowledge, gene editing may present issues that are still unresolved.

An international moratorium was announced on clinical use of human germline editing which does not allow creation of genetically modified children and allows time to debate about the moral, ethical, scientific, societal, legal issues and to establish regulatory frameworks that would govern the technology[2] (NAS, 2015). There is a gradual move to open up but there have been a few scandals such as the birth of the twins in China with the gene edited for HIV which was looked down upon by the world. Even though considered a scientific advancement, it was determined to be ethically and morally unacceptable. It was criticized and outrightly rejected by the scientific communities since investigators had faulted on many accounts such as safety assessments, ethics review, informed consent etc (Regalado, 2019; Kleiderman and Ogbogu, 2019). This example clearly highlights the importance of having a governance and monitoring framework and ensuring that scientific research is carried out in a manner that is socio-culturally acceptable and relevant to serve societal values and customs. There is an added responsibility to allay fears, such as those, that may be related to irreversible changes in germline, inaccurate gene editing, off target mutations, deleterious mutations, unknown affects, implications for future generations, interaction with other genetics variations or even environment the high chances of being misused for prenatal testing, damaging further sex ratio, unmonitored and unreported fetal manipulations, ethics of creating designer children, eugenic manipulations, enhancement, commodification and possibilities of exploitation of sorts (NAS, 2017).

Integrating Ethical Considerations

Ethics plays an important role in improving scientific value of research and its translation to public good. Integrating the ethical principles and values

would go a long way in imparting protection to research participants and improving quality of research outcomes. The objective of an ethics review process is to look at both science and ethics to guide the researcher to better conduct of a research study which has social value, ensures safety and well-being of participants, protects their rights, involves monitoring and avoids undue harm. It must also provide an opportunity to participants for better understanding, as well as autonomous decision making (ICMR, 2017). It is therefore important that research involving gene editing be carefully reviewed by an ethics committee which is competent, updated, timely and independent in its review and decision making processes. The suggestions from an ethics committee can improve the study design conduct and its outcomes as well as impart better protection to the participants. At the present moment the promise of benefit in terms of its therapeutic potential looking at curing diseases is huge but so are the associated risks and long term outcomes mostly due to use of a novel technology. It still remains to be seen how the benefits will be balanced in a manner that the benefit risk ratio is in favour of the mankind. How can gene editing be used safely so that benefits can be assured and risks can be minimised? This is the question that needs to be answered now.

There are number of unclear risks of the technology at the moment and many of these are unknown and unproven at the present state of knowledge. Use of technology should also ensure that there is no exploitation of any person or community and appropriate counselling and consenting processes are in place to protect the people. This becomes even more important when dealing with persons who belong to the vulnerable category, which could be due to their disease, condition, age or lack of understanding due to their profile. These persons need additional protection not only for their safety as they may not be in a position to protect their own rights but also their autonomy. For all participants, the privacy and confidentiality aspects need due consideration as genetic research commonly can result in stigma and discrimination (Tavan, 2004). A small leak of information about a genetic condition, can lead to ostracisation of individuals as well as their families by their communities and also have implications related to be denied health insurance or even employment. Any identifying information of the persons has to be properly safeguarded and clinical records be filed carefully with access limited to only select authorised persons. Any collaborative research

where data sharing is needed must also take care of the concerns related to personal clinical information of the individuals who are part of this work.

Counselling and Informed Consent

An appropriately informed and understood consent is an important requirement and must be carried out in a manner that improves voluntary decision making without any undue influence or coercion to force participation. This is the basic requirement for any kind of biomedical research, however these considerations become all the more important when dealing with any new technology. The explanations should be made in a language and manner that is easily understood. Terminology used in genetics is usually not simple to understand and technical jargon that can easily be misinterpreted if not explained well. Genetic testing or interventions must always be accompanied with a pre and post counselling in a non-directed fashion to explain the available choices, limitations, probable outcomes, to facilitate good discussion, understanding and a voluntary informed consent after an opportunity has been given time to discuss with family or friends, without any undue pressure or coercion to agree to participate. There should be ample opportunity provided to decline from participating and even if agreed to once, be free to withdraw from the research at any time. It is important to share information related to possible side effects, many of which may be unknown in light of the existing knowledge. It may not be simple to explain gene editing and how it may impact life in the long run as there are many unknowns at this point of time.

However, this should be seen as an opportunity to discuss openly and allay fear or doubts and truthfully reply to any queries. The process should not be rushed and there should be ample time and opportunity in private to discuss this in detail. The engagement must be done in a culturally sensitive manner and in a language that is well understood and preferably by someone, who could even be a genetic counsellor, or a lead investigator who can devote time to patiently and correctly reply to all questions as per need. The informed consent is a process and not just signing a sheet of paper and the interaction has to continue for the duration of participation and even when the study is over. And once the results are available they need to be explained to the individual as reports stating genetic variations/ mutations/ genome sequences and gene edited or modified sequences, and

their implications would hardly be understood. Any new findings and the implications of the same on the health of the individual or the family must be explained.

Transparency and Accountability

New Technologies come with an inherent challenge, in view of lack of complete understanding as well as fear of their long term implications. There is need to clarify who will be accountable in case of an unforeseen untoward event, what happens after. As a good ethical practice, it is important to understand and implement responsible use of gene editing technology and to have provisions in place to safeguard, provide medical management and compensation for any research related harm. All procedures and processes followed for gene editing processes should be as per approved protocols, and efforts should be there to ensure transparency and accountability. Before implementing, all protocols must undergo thorough scientific and ethics review, peer review process to ensure latest understanding and to the extent possible, this information should be available in public domain. All involved stakeholders have the joint responsibility to ensure that the safety and well-being of participants is ensured and risks are minimised. The research results once available must be quickly published in science journals whether the results are positive or negative and also be available on public databases such as Clinical Trial Registry of India (CTRI)[3]. Efforts must also be made to disseminate results and facilitate translation of these outcomes for the benefit of others. This can only be built and improved over a period of time. As science moves forward, there is a need for an ethical framework that facilitates socially relevant research and open dialogue, transparent processes, accountability and good communication amongst various stakeholders regarding use of genome editing technology seeking solutions towards improvement in human health (Mathur, 2018).

Communicating Science and Building Public Trust

The connection between science and society is of paramount importance and unless this societal connection is made, even the best of science would not be able to deliver and to bring about a change to betterment. The ethical issues related to gene editing have to be handled upfront to reap the full benefit and communication has to be improved and to be carried out in a

manner that it is easily understood by masses. Communicating science effectively required skills, interest and initiative to unfold its complexity (Fischhoff, 2019). The issues related to gene editing require a detailed discussion between researchers, clinicians, bioethicists, philosophers, ethics committees, legal experts, religious leaders, social scientists, civil society, patient representatives, members from press, agencies, sponsors, policy makers and others. Therefore, to make this work, as we evolve and learn to apply this technology for human betterment, efforts have to be in place to understand, connect, rightfully communicate, engage with the society and have a public discourse so that all pros and cons can be debated upon. This needs fair, honest and open discussions and utilising available platforms for advocacy. The need of the hour is to understand the local traditions, customs, or religious beliefs that may influence public opinion. An open dialogue will help to improve understanding, allay fears, clear doubts and eventually help to build trust in the technology. Usually, scientists develop technologies in the lab, publish their findings and then there is a disconnect with the society since these results are only available to a small audience who reads science journals and not available to the public at large. Efforts have to be made to connect with the masses, by translating these findings in simple form or manner so that they are useful for a much larger audience. All stakeholders must come together to find ways of engaging with the public and this has to begin right at inception of the project. They must discuss upfront details of plan, expected results, possible limitations, ways of sharing results and long term plans for translating outcomes to public health benefits. In addition, a discussion on ways of tackling mistrust, dispelling unnecessary fear and building positivity must be undertaken. An important consideration is also the fact that public trust cannot be built overnight and the engagement is a process which depends on how often and how well the scientists communicate, respond to and engage with public in a language and manner that is understood. Some of the approaches that are helpful are; having open public debates at regional level, wider consultations with stakeholders, developing advocacy material in simple language, engaging with print as well as social media, through newspaper articles, or the TV channels etc. Considerable amount of effort is needed to really do a good communication which helps to build public trust for both science as well as research community at large.

Ensuring Access to Technology

Another important consideration is to identify plans to make sure that the gene editing technology would be accessible to people who need it. At present one doesn't know well, if this is going to be a very expensive technology and be available to the very select few who may reap the advantage (Mittal, 2019). Would it really be ethical if the technology has limited access to few privileged by their position and the general population is largely unaware and with limited resources to access this. It is important to discuss what uses of technology can be permitted and for whom? How will people be able to access these? What are the pathways to ensure equitable access? For it to be ethical, the powerful techniques should not only be available to the most powerful but to the common man. The issues related to access should not lead to further widening of the gap between those who can or cannot afford to have it. On one hand is the challenge to make technology acceptable and to remove the unwarranted scare and on the other to ensure that the technology is used for betterment of many and not just the elite. Investments are needed to facilitate development of technologies that will not only be accessible but also be available at affordable costs to those who need them. In India a lot of support is expected from the government agencies as well as other sponsors for research so that science can evolve in the labs and in parallel efforts can be initiated to educate, train and develop advocacy methods to create better understanding which will eventually help in improving its acceptability.

It is also important to see that India progresses ahead and will be in a position to cater to the needs of the country when the fruits of research have ripened. There is an angle of commercialisation and profiteering from the technology as most of the genetic workup comes at huge costs and is not easily available but at very few specialised centers. Even though the technology in itself may not be expensive however, there is enormous interest amongst private players due to its commercial potential towards treatment of variety of serious genetic ailments, cancers and other polygenic diseases. As science moves on to offering personalised medicine to human beings, the technology runs the risk of being used for only those who can afford this. All of these issues need discussion on a wider platform to safeguard ethics, equity and access to novel methods to improve human health.

Capacity Building & Collaboration

There are few institutions that have the infrastructure and mandate to undertake intensive research related to gene editing. Unless there are more opportunities the technology will remain limited to influential and there will be limited trained manpower available to work around novel research methodologies. The institutions need to provide a supportive backing with an environment that cultivates and nurtures cutting edge research, provides an environment for innovative work, independence to undertake scientific explorations, and infrastructure to commit to this cause. The support from institutions in terms of their policies and leadership is important to provide encouragement to undertake research, scientific and technological developments. Research may require investments for lab work and also to build in opportunities for mentoring, training, collaborations, sharing of resources, joint research programs, platforms for exchange of ideas. Collaborations between partners to have clear objectives, areas of cooperation, roles and responsibilities, sharing of data, publications, patents and other such considerations (NAS, 2017). They should also take care that any biological material and data sharing on global platforms or other observatories takes care of individual privacy issues. The country must build its capacity to work on gene editing and eventually to develop the connections for bench to bedside translation involving medical professionals. A lot of efforts are now needed to initiate dialogue, foster collaboration and trust amongst all stakeholders. Being a new area, there may be need to train more scientists and medical professionals to join hands to develop methods that can improve human health following the right regulatory and ethical procedures.

Ethical and Regulatory Governance Framework

There are several stakeholders who are connected with the governance of Gene Editing. It is not only the researchers, but ethics committees, institutions, sponsors, regulators, government agencies and all others involved in review, monitoring, funding research. The governance framework should be developed in a manner that it supports quality research, helps to translate benefits to the population, regulates, monitors and safeguards the interest of the population. There is need to initiate a discussion to understand

the type of frameworks needed to regulate the technology to promote use that serves the public interest. Even though there are no direct regulations, however, there are existing guidelines and regulations that would facilitate mechanisms to govern gene editing research and applications. The ICMR National Ethical Guidelines, 2017 have discussed the ethical aspects that need to be considered while using gene editing technology (9). All clinical trials for product development need to follow the New Drugs and Clinical Trial Rules, 2019 which have provisions that will allow for regulation of the new technology by *Central Drugs Standard Control Organisation* (*CDSCO*) and govern the conduct of clinical trials for use of any new technology on humans (CDSCO, 2019). Also ICMR and DBT have jointly brought up a new National guideline document on gene therapy, product development which provides description of requirement for the research and clinical trials (ICMR-DBT, 2019). The guidelines have also given a flow chart to explain the step wide procedures to be followed including review by the DBT committee on gene/ genetic modification and the Institutional biosafety committee which is involved in oversight. As of now the germline gene, therapeutic and gene editing for therapeutic purposes, in utero gene editing is prohibited in India and somatic cell gene editing can be pursued as a clinical trial study. The applications will need the approvals of various committees before being submitted to the CDSCO to be carried out as a clinical trial with a pre-clinical and clinical research model. The existing frameworks can be further tailored and strengthened to support research and use of gene editing technology. There is a need to develop the expertise and the capacity within the regulatory system to handle gene editing related concerns and guide against potential misuse. The government needs to make the right investments now, to support good research through grants, ensure quality outcomes and putting into action an appropriate ethical and regulatory framework for monitoring this technology.

Conclusion

In pursuing gene editing, the first step is to build bridges between science and society through pathways guided by ethical values to developed a framework. The importance of increasing awareness of various aspects of gene editing is important not only among public also but also amongst other stakeholders such as clinicians, researchers, regulators and agencies.

Being a new subject, education as well as understanding even among medical fraternity would be limited and efforts are needed to change this and promote research. This is an ever evolving field and we need to learn as the science evolves and there are new global experiences that would guide evolution of guidelines and regulatory framework. Pursuing state of the art quality research in the country can bring out safe affordable accessible reliable technology in future which can be made available to common man at affordable costs. The approaches have to be humane to serve societal interest and efforts be made to keep coming up with the advancement in technology to put it to full use through adequate engagement and communication. It is time that this topic is discussed openly so that the fruits of this technological advancement can be reaped by our population.

Endnotes

1 Genetic scissors: a tool for rewriting the code of life. 7 October 2020. The Royal Swedish Academy of Sciences Nobel Prize in Chemistry 2020 awarded to Emmanuelle Charpentier & Jennifer A. Doudna "for the development of a method for genome editing". https://www.nobelprize.org/prizes/chemistry/2020/press-release/

2 Eric Lander, Françoise Baylis, Feng Zhang, Emmanuelle Charpentier, Paul Berg and specialists from seven countries call for an international governance framework. Adopt a moratorium on heritable genome editing. 13 March 2019.

3 Clinical Trial Registry of India (CTRI). http://ctri.nic.in/Clinicaltrials/login.php

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From Genome Editing to Battling a Pandemic: The Rise of CRISPR

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Abstract: An accidental discovery followed by a series of systematic investigations led to the understanding of the function of CRISPR-Cas as an adaptive immune system in bacteria. Soon, the functioning of CRISPR-Cas, that utilizes an RNA guided Cas protein to target and degrade nucleic acid, was worked out. The CRISPR-Cas system was soon harnessed for manipulating nucleic acid sequences *in vitro* and *in vivo*. The specific nuclease activity of Cas opened broad avenues for genome editing and a whole range of other applications in molecular biology research, molecular diagnostics, biotechnology, crop improvement and therapeutics. COVID-19 pandemic saw the rise of CRISPR based diagnostics paving a way forward towards a robust, cost effective and rapid point-of-care diagnostic assay. The short duration that went into developing and deploying these assays makes it possible to develop rapid testing for multiple other genetic and infectious diseases. Some of the challenges that need to be overcome before CRISPR-Cas can be used for gene editing and genomic control include the delivery method to take CRISPR-Cas system inside the cells, requirement of a PAM sequence to target and the off-target effects that are seen besides the occasional chromosome breakages that have been observed while performing in vivo studies. Systematic protein engineering for CRISPR-Cas system and discovery of other orthologs of already known Cas proteins would help in overcoming some of these obstacles in near future.

Keywords: Genome-editing, CRISPR-Cas, COVID 19, Diagnostics, FELUDA.

Discovery of the CRISPR-Cas system

The discovery of CRISPR dates to 1987, when 29 nucleotide repeat sequences interspaced by 32 nucleotide unique sequence was reported downstream of alkaline phosphatase gene of Escherichia coli (Ishino et al. 1987). It was Francisco Mojica in 1993 who next found palindromic

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repeat sequences of 30 base pairs separated by spacers of 36 bps, in a high salt tolerant archae bacteria, *Haloferax mediterranei*, (Mojica et al. 1993). These repeats did not match with any of the known family of repeats in prokaryotes. Soon, similarly structured but not similar/identical repeats were found in other distantly related prokaryotes as well suggesting that they served some important function (Mojica et al. 2000). These were later named as clustered regularly interspaced palindromic repeats (CRISPR) (Jansen et al. 2002; Mojica and Garrett 2013). Further characterisation of this locus found specific CRISPR associated (Cas) genes in the vicinity of the repeats (Jansen et al. 2002).

It was not until 2003 that the function of CRISPR became evident when Mojica found the spacer sequences present in a strain of *E. coli* to match with that of P1 phage that infects multiple *E. coli* strains. This *E. coli* strain that harbored the P1 phage sequence was also known to be resistant to P1 phage infection (Mojica et al. 2005). It was then that the idea of CRISPR being an adaptive immune system of prokaryotes started to take shape in Mojica's mind. The proof for which came soon by Philippe Horvath's work on *Streptococcus thermophilus*. They selected for phage resistant strains of the bacteria and found that the spacers of CRISPR loci in the resistant strains had phage acquired sequences. Additionally, they found that Cas9 was also necessary for phage resistance and since it harbors two nuclease motifs (HNH and RuvC), it would expect to cut nucleic acids (Bolotin et al. 2005; Makarova et al. 2006; Barrangou et al. 2007). Now that the function of CRISPR-Cas was established, next step was to see if it can be programmed to harness its power of recognition and targeting of phage sequences to make prokaryotes resistant to infections by these specific phages.

John van der Oost and his team discovered CRISPR RNA (crRNA) that was transcribed from the CRISPR locus, these sequences started with last 8 bases of the repeat followed by the spacer sequence and the next repeat. By creating synthetic crRNAs, they could target lambda phage genes and made bacteria that carried these crRNAs resistant to the lambda phage (Brouns et al. 2008). Their experiments also pointed to the target of these crRNAs to be DNA and not RNA (or mRNA). Luciano Marraffini and Erik Sontheimer provided the proof that it is indeed DNA and put forth that CRISPR is a programmable restriction enzyme (Marraffini and Sontheimer 2008).

Soon, Sylvain Moineau and his colleagues provided the evidence that Cas9 cuts DNA at specific sites which is guided by the crRNA. This discovery was made possible by studying plasmid interference in *S. thermophilus*, where they found linearized plasmids in some inefficient strains of the bacteria, which on sequencing revealed that there was a single blunt edge cleavage happening 3 nucleotides upstream of proto-spacer adjacent motif (PAM) (Garneau et al. 2010). PAM was earlier characterised by Philippe Horvath and Sylvain Moineau to be a sequence present in the target DNA, which is essential for the CRISPR-Cas to function (Deveau et al. 2008; Horvath et al. 2008).

Emmanuelle Charpentier and Jörg Vogel found an abundant class of RNA in *S. pyogenes* that was transcribed from adjacent region of CRISPR locus and was complementary to the repeat sequence of CRISPR (Deltcheva et al. 2011). This complementarity in this recently discovered trans-activating CRISPR RNA (tracrRNA) suggested that tracrRNA would hybridize with crRNA precursor and thus required for processing crRNAs, which they next demonstrated experimentally to be the case. This implied that tracrRNA was also an important component of CRISPR-Cas along with crRNA and essential for its functioning (Jinek et al. 2012).

Soon, Virginijus Siksnys could show that transferring the *S. thermophilus* CRISPR system in *E. coli*, which is a distant microbe, was possible and it was fully functional in *E. coli*. They next performed in vitro experiments with spacer sequences of their choice and demonstrated that the system could cleave DNA *in vitro* at a specific site that they had chosen (Sapranauskas et al. 2011). They also showed that purified Cas9 protein can be used with in vitro transcribed crRNA and tracrRNA for the CRISPR system to work (Bolotin et al. 2005; Makarova et al. 2006). Emmanuelle Charpentier and Jennifer Doudna also demonstrated the same, but they went on a step further to show that crRNA and tracrRNA can be fused into a single guide RNA (sgRNA) (Jinek et al. 2012). Both the groups, therefore, opened avenues for various biotechnological applications using CRISPR-Cas. One important experimental evidence that was needed to apply CRISPR-Cas for gene editing was to demonstrate that it would work in mammalian cells too, which came in 2012. It was Feng Zhang who used Cas9 tracrRNA, and a CRISPR array to target 16 different sites in human and mouse genome and thus provided the first proof-of-concept that it is indeed possible to target genes in mammalian cells with CRISPR-Cas (Cong et al. 2013).

Applications of CRISPR-Cas system beyond genome editing

Genome Editing

With a system in hand that can target a specific sequence using a single guide RNA, the avenues of genome editing got expanded. CRISPR-Cas could thus be employed for gene deletions or gene insertions in any cell type (Doudna and Charpentier 2014). One such example came from a butterfly species wherein a bi-allelic knockout was shown to have a lighter wing color than the wildtype butterfly (Li et al. 2015). This illustrated the successful implementation of CRISPR-Cas for gene deletion in generating a knockout. While there are multiple examples for gene deletion in diverse animal models ranging from *Candida albicans*, zebrafish (Xiao et al. 2013), mouse (Zhou et al. 2014), and rabbits, the gene insertion examples are rare. Transgenic pigs have been reported wherein gene insertion at a specific locus, which also serves as a safe harbour for stable expression of the gene inserted (Ruan et al. 2015). The reasons for this paucity of experimental data for gene insertions in animals highlights the challenges (discussed in later section) that still need to be overcome before we move to successful gene editing for the correction of disease-causing mutations.

The above examples of gene deletion and insertion rely on the nuclease activity of Cas protein to cause double strand break (DSB) at the specific locus identified by sgRNA and further dependent on non-homologous end joining (NHEJ) or homologous recombination for the deletion or insertion to occur (Bennardo et al. 2008; Gaj et al. 2013; Decottignies 2013). There is another method to bring about change in the sequence of the gene that is more feasible and relevant for correcting single point mutations and that is the use of base editors. A sgRNA: dead Cas (catalytically inactive, does not cause DSB) complex can guide the base editor (like cytidine deaminase or adenosine deaminase), which is conjugated with the Cas protein, to the specific site for conversion in this case from C→T or G → A (Komor et al. 2016; Nishida et al. 2016). Successful base editing using CRISPR-Cas system has been demonstrated in not just animal models like zebrafish and mouse embryos but also in human embryos which takes us a step closer towards use of CRISPR for gene therapy (Kim et al. 2017; Rossidis et al. 2018; Liang et al. 2017).

Preclinical trials using CRISPR-Cas have shown successful gene silencing *in vivo*. In mouse models, silencing of Pcsk9 to restored cholesterol homeostasis (Ding et al. 2014) and disrupting *Nrl* gene in retina to control retinal degeneration (Yu et al. 2017) demonstrated the successful delivery of CRISPR-Cas machinery and manipulation of target genes. The next step after preclinical testing is translation into clinics for human trials. Some of the human clinical trials which are under way include treatment of genetic diseases like β-thalassaemia and retinal degeneration that can cause blindness (Maeder et al. 2019).

Targeting RNA

Some of the Cas proteins recognise RNA instead of DNA thereby creating opportunities for targeting of RNA and expanding the scope of CRISPR-Cas beyond DNA targeting. Cas13 and FnCas9 identify RNA sequences (Price et al. 2015; Abudayyeh et al. 2017; Cox et al. 2017)and can be deployed in visualisation of RNA or for generating RNA binding proteins that would help in detection of RNAs. SaCas9 and *Campylobacter jejuni* Cas9 cleave RNA in a crRNA dependent but PAM independent manner, thus can be utilized for targeting and degradation of endogenous mRNAs (Strutt et al. 2018; Dugar et al. 2018).

Catalytically inactive SpCas9 has also been programmed by using PAMmer, PAM sequence in the oligonucleotide that recognises RNA exclusively and not the DNA that encodes for this RNA sequence. This programmable RNA targeting Cas9 known as RCas9 used to track mRNAs in live cells (Nelles et al. 2016). Catalytically active RCas9 can be used to target ssRNA and degrade them which would have therapeutic applications exemplified by degradation of mRNAs in microsatellite-repeat expansion diseases (Batra et al. 2017). Base editors can also be fused with RCas9 to modifying the transcript directly to rectify disease causing mutations instead of targeting the genomic DNA.

Genomic Control

Besides the editing of genome/transcriptome, it is also possible to suppress or activate specific genes by using CRISPR-Cas. Utilising the dead (catalytically inactive) Cas (dCas) fused with transcriptional repressors

like KRAB domain or transcriptional activators like p65, it is possible to repress or activate specific genes (Gilbert et al. 2013; Gilbert et al. 2014). Not just the genome can be controlled in this manner but also the epigenome can be modified by using Cas9 fused with catalytic domains of acetyl transferases or methylcytosine dioxygenase TET1 to acetylate or methylate histones of specific loci (Kearns et al. 2015; Hilton et al. 2015). The demethylation approach has been used for the treatment of Fragile X Syndrome by demethylating the CGG expanded repeat in the 5'UTR of FMR1 gene, thus causing gene expression (Liu et al. 2018).

Antimicrobial and Antiviral Agents

CRISPR-Cas can give rise to sequence specific antibiotics which can target bacteria using nuclease activity of Cas9. This type of antibiotic has been shown to be effective against bacterial populations to selectively destroy pathogenic bacteria (Beisel et al. 2014; Gomaa et al. 2014; Bikard et al. 2014). CRISPR-Cas not just protects bacteria from phages generating a phage vaccine but can also be deployed for targeting of viruses that infect humans. HIV-1 (Hu et al. 2014; Ye et al. 2014; Liao et al. 2015), herpes (Wang and Quake 2014), Hepatitis B (Kennedy et al. 2015) are some of the viruses against which development of CRISPR-Cas based antivirals is underway.

Crop Improvement

Crops of agricultural importance have been engineered and bred for long to modify various traits; CRISPR-Cas has made it faster for these manipulations. Crops are being engineered for higher yields, draught resistance, resistance against plant pathogens, and better nutritional properties to name a few. Corn has been manipulated by CRSIPR-Cas to generate chlorsulfuron (an herbicide)-resistant plant (Svitashev et al. 2015). Targeted mutagenesis has also been successfully demonstrated in soyabean (Li et al. 2015).

Bacterial manipulations for industry

CRISPR-Cas is being used in industrial applications for genotyping, vaccination of bacteria against bacteriophages, and generation of probiotic cultures for yogurt and cheese (Barrangou and Horvath 2012; Barrangou et al. 2013). It can be used to generate biofuel (Ryan et al. 2014) and

biomaterials from industrial microbes (bacteria, yeast and fungi).

Biological Control

CRISPR-Cas can be used in bringing about changes at the population level of an organism that is exemplified using gene drives in *Anopheles gambiae* (causative agent of malaria) to cause sterility of female mosquitoes (Hammond et al. 2016). Gene drives carry trait specific genes along with CRISPR-Cas9 machinery and can rapidly spread the trait to a population (Esvelt et al. 2014).

Diagnostics

With CRISPR-Cas, diagnostics have been revolutionized by the development of point-of-care tests that are rapid, accurate and affordable. Detection of diseases that were dependent on expensive sequencing can now be done without the need of sequencers because of the deployment of CRSIRP-Cas. The specific detection of target DNA/RNA sequences by sgRNA-Cas complex creates the specificity and accuracy in the2se tests. Some of the Cas proteins that have been adapted to detection systems for infectious and genetic diseases include, Cas12a, Cas13 and Cas9.

Cas12a cleaves sequence specific dsDNA (generated via amplification from the patient samples) that activates trans activity of Cas12a, which then non-specifically cleaves ssDNA and if that ssDNA is bound to a reporter or a fluorescence tag then the fluorescence signal generated on cleavage of the reporter would tell us the presence of the specific viral sequence like that for HPV, which has been detected using this assay (Piepenburg et al. 2006). This system was named as DNA endonuclease targeted CRISPR trans reporter (DETECTR). By amplifying the DNA using isothermal PCR abrogates the need for a thermocycler, thus making detection truly a point-of-care assay.

Cas13 based assay called as SHERLOCK (specific high-sensitivity enzymatic reporter unlocking) also uses isothermal amplification combined with sgRNA:Cas13 based detection of specific RNA sequence. This identification and binding of Cas13 activates the collateral nuclease activity of Cas13 which can now cleave any ssRNA that can be coupled to a fluorescence reporter (Gootenberg et al. 2017). The assay has been successfully deployed for the detection of infectious viruses like Zika virus.

One of the Cas9 based detection platform that was developed in India is FELUDA (FnCas9 editor linked uniform detection assay) that utilises the binding specificity of dead FnCas9 and combines it with lateral flow detection using biotinylated substrate binding to the lateral flow strip and visualisation via binding of gold nanoparticles (Azhar et al. 2021). Because of the burden of sickle cell anemia in the country, the need for a robust, inexpensive, and highly specific point-of-care assay was there. FELUDA fulfilled that need by accurately detecting SCA with specificity and sensitivity equivalent to that of sequencing.

Role in Battling COVID-19

The end of 2019 brought with itself unforeseen circumstances for the entire world with the spread of SARS-CoV2 throughout the world in a matter of a few months. Testing and contact tracing became of paramount importance as the corona virus had evolved itself to be transmitted through asymptomatic carriers, creating a scenario of fear and uncertainty all around. The early diagnostics for COVID-19 relied on RT-PCR based detection of SARS-CoV2 from patient samples, but soon the limitations of RT-PCR were becoming evident. The test required specialized personnel, proper lab space and a real time PCR machine that was not accessible at all places and even when they were accessible the labs soon were getting overwhelming number of samples making it impossible to finish the entire protocol of 1.5 – 2h (RNA isolation followed by reverse transcription and real time PCR) on time. This meant days for some of the samples to be tested and unless the suspected patients would spend time in isolation the disease would be further transmitted. While the diagnostic system was collapsing it was CRISPR-Cas based diagnostics that came to the aid of the world.

The timelines that went into developing CRSIPR-based assays for COVID-19 illustrated the years of hard work that was invested in understanding and harnessing the abundant potential of CRISPR-Cas for molecular diagnostics. Soon, SHERLOCK, DETECTR, and FELUDA among others were adapted for the detection of COVID-19 (Rahimi et al. 2021). All these provided point-of-care, inexpensive, robust, and rapid assays with a sensitivity and specificity matching that of RT-PCR. The second wave that hit most nations saw the emergence of variants of SARS-CoV2 virus and detection of which was completely dependent on genome

sequencing. CRISPR-Cas came to the rescue again by adapting FELUDA into RAY (Rapid Variant AssaY) which could identify specific variants without the need for sequencing (Kumar et al. 2021).

All this put together is a huge achievement for the entire scientific community to show preparedness at a time when the whole world was unprepared.

Prospects and Challenges

Although, CRISPR-Cas proved its value in challenging times, but there are still challenges that exist which hinder the achievement of true potential of CRISPR in genome editing and therapeutics. Some of these challenges include delivering of the CRSIPR-Cas machinery into the eukaryotic cells *in vivo* and reducing the off target effects that could lead to disastrous effects like breakage of chromosomes (Leibowitz et al. 2021). With the discovery of orthologous Cas proteins and engineering of more effective variants of Cas proteins some of these issues are being actively addressed. The dependance on a PAM sequence for the targeting of nucleic acid, which limits the use of CRISPR-Cas to a restricted number of sequences has been overcome to some extent by modifying and simplifying the PAM sequence and thereby broadening the scope of targets that can be manipulated by CRISPR (Kleinstiver et al. 2015; Ma et al. 2019). The possibilities and avenues that CRISPR-Cas as a molecular tool opens up are limited only by our imagination and we will be entering into a new dawn for molecular biology as the full potential of CRISPR will be realized.

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Perspective

Ethics and Genome Editing : A Perspective from Europe

European Group on Ethics in Science and New Technologies, Brussels*

Ethics of Genome Editing^

The advent of new genome editing technologies such as CRISPR/CasX has opened new dimensions of what and how genetic interventions into our world are possible. The European Group on Ethics in Science and New Technologies (EGE) addresses the profound ethical questions raised and revived by them in its Opinion on *Ethics of Genome Editing*.[1] The Opinion analyses various domains of application, from human health to animal experimentation, from livestock breeding to crop variety and to gene drives.

With its wide view across areas, it identifies underlying and overarching issues that deserve our concerted attention, among them, the different meanings that ought to be attributed to humanness, naturalness or diversity. This enables conclusions that provide panoramic perspectives complementing narrower, area-specific analyses. In the same vein, the Opinion is concerned with the global dimension of genome editing and its regulation and formulates recommendations with a particular focus on the international level. Its main overarching considerations are the following:

- How the human ability to edit the genome should be regulated is closely linked to questions about the status of humanity in 'nature'. Are we its masters with a right to transform it, or are we one of many

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^ This is a summary of the EGE's Opinion on "Ethics of Genome Editing" and was first published by the European Commission in April 2021

[1] https://ec.europa.eu/info/publications/ege-opinions_en

parts of it that all thrive in relation to each other? Does our growing knowledge about it postulate that we care for it and protect it where we can? Awareness of one-sided positions, such as anthropocentrism and speciesism, can help us to engage in the debate about genome editing on the basis of the values of diversity, respect and responsibility.

- The application of genome editing in human and non-human animals raises questions about what defines us as humans and what distinguishes species from each other. Our genome is often taken as foundational of our humanness, providing us with distinct capacities. Should we, or should we rather not, experiment with the delineations defining and distinguishing species? What risks and responsibilities would this entail? On the other hand, genetic exceptionalism and determinism (the idea that the genome plays the central role in shaping who we are and determines our behaviour) can prevent us from taking a more holistic perspective on the many factors defining us and our lives, as well as other species and theirs. Awareness of this can help us to put genome editing and discourses about it into perspective.
- Diversity, human diversity and overall biodiversity, can be impacted by genome editing in different ways. The technology may both offer possibilities to preserve and diversify biospheres, and come with risks of reducing genetic pools and, hence, diversity – both in biological terms and in terms of what kind of diversity is socially appreciated. This requires us to reflect about the responsibilities of humans towards other species and the planet, most importantly as regards anthropogenic climate change; as well as towards other humans, as regards determining what kinds of persons a society might want to have and what specific variations are, or are not, a problem in need of a genetic, technological 'solution'. When thinking about diversity and genome editing, we therefore also need to think about freedom, autonomy and risks of oppression and marginalisation.
- The focus on the broader picture of the Opinion also raises awareness of the risk that genome editing could be hailed as a technological solution for issues of social nature. An approach that does not consider the ethics and governance of genome editing in a technology-specific way enables us to pinpoint the broader societal questions in the realm of

which technologies, or socio-technical systems, can have an impact. What world do we want to live in and what role can technologies play in making it reality?

- Debates about genome editing often focus on the question about the conditions that would render it 'safe enough' for application. The Opinion draws attention to the importance of nuancing and resisting this framing, as it purports that it is enough for a given overall level of safety to be reached in order for a technology to be rolled out unhindered, and it limits reflections on ethics and governance to considerations about safety. Much to the contrary, ethics should serve to tackle broad governance questions about how technologies can serve our common goals and values, and not be limited to providing a 'last step' of 'ethics-clearing' of a technology. Safety, if to be a safe concept, must be framed in its broadest sense, including psychological, social and environmental dimensions, as well as questions about who gets to decide what is safe enough, and by which processes.
- With the increasing adoption of genome editing, claims were made that scientists were not only able to 'read' the 'Book of Life', but also to 'write' it and 'edit' it. Any words that are chosen to describe a new technology have an impact on the discourse about it. They shape how we perceive it and engage in debates about it, they frame what questions scholars ask about it and investigate, they influence how policy makers respond to it. Awareness of this can help us to find terms that appropriately capture and transmit the complexity of new genome editing applications and of the ethical questions they raise.

The Opinion begins with an overarching chapter assessing the preceding points and continues with detailed ethical analyses of pertaining questions in the main areas of application of genome editing. Some of the key reflections of those chapters are the following:

Genome editing in humans

If the genome of one human being can be submitted to deliberate, targeted editing by another human being, what implications does this have for the relationship between the two persons? Would this undermine the fundamental equality of all human beings, or is it necessary to assume

the responsibility of such an intervention when it can help to prevent a serious disease? In this context, we often distinguish between therapy, prevention and enhancement, as different purposes that genome editing can serve, with the use of genome editing for purposes of therapy or prevention of disease being by many considered far more acceptable than the use for enhancement purposes.

While somatic genome editing therapies have been developed for decades, there appears to be general agreement that germline genome editing, hence introducing heritable changes, is not to be applied at this point. In many fora have its potentially severe risks– for the individuals concerned and for society overall – been discussed. Together with the difficulty to conduct long-term studies and the availability of alternative methods for avoiding heritable disorders, they require us to ask: Are research on embryos and the risk of harm caused by the technology ethically acceptable and proportionate for the few cases for which there is no alternative solution? Questions like these require broad and well-informed societal deliberation on the basis of an awareness about how heritable genome editing may result in major changes of a society overall, its composition and its values.

Genome editing in animals

Animals can be considered by humans as having an intrinsic value in their own right, or they can be considered in their instrumental value for humans. Against this background, genome editing revives old questions about inter-species relationships and relational values. In what is the intrinsic value of non-human animals different from that of human animals? How do we define respect for non-human animals and what rights do we attribute to them?

In human health research, genome editing might on the one hand offer opportunities to replace animal experimentation with alternative laboratory methods; on the other hand, the mere ease of creating genome edited animals with the precise genetic traits useful for a given research purpose could also lead to an increase in their use. Genome editing in research animals moreover raises questions about animal welfare, for example if traits

leading to disease are introduced; about de-animalisation, if traits that are natural for a species are knocked out; about humanisation, if non-human primates (or other animals) are genetically changed in a way so that they resemble humans more than they would naturally do; and about justice if the technology would serve exclusive scientific and commercial health services, for example in the context of xenotransplantation.

In farm animals, genome editing applications largely serve the same goals as selective breeding practices, namely, to increase yields, strengthen disease resistance and improve product quality. Ethical considerations in this context relate to animal welfare, biodiversity, sustainability and the necessity of an unbiased public dialogue. Genome editing has the potential to facilitate or exacerbate commercial practices in livestock breeding that are already highly contested.

Genome editing in plants

Current forms of agriculture contribute significantly to the anthropogenic climate crisis. There is a need to ensure food security, provide renewable resources for fuel, feed and fibre, safeguard the retention of biodiversity and protect the environment. Genome editing technologies could, with appropriate and proportionate control, enhance our ability to achieve these goals, just as they could result in the opposite without it.

Social and justice considerations play a role in this too. The economic impact of choosing to use or not use plants produced with new genome editing technologies may be significant and public authorities should ensure that society overall benefits. This includes that small farmers and holistic approaches to production are supported; that new varieties will not result in greater industrialisation leading to increased unemployment and precariousness in agriculture; that the ability of small companies and research organisations to produce new varieties is strengthened and monopolisation of the production of seed restrained and prevented.

In Europe, genetically modified food is contested in large parts of society. This can be attributed, in parts, to mistakes made in the past in not involving the public in choosing what was introduced onto the market, as well as a lack of safeguards preventing false information or hype provided by all sides in the debate.

Gene drives

Gene drives are a specific use of genome editing that has drawn particular attention as it offers the possibility to guide 'biased' inheritance of certain genes into entire animal or insect populations, for example pests or mosquitos, usually with the aim to make them harmless or more vulnerable. This raises a number of ethical concerns that have been discussed in various fora. Among them are also important concerns about global and epistemic justice, as well as anthropocentrism: If one day applied, how can we ensure that those populations that need it the most have access to the technology? How can we ensure that we solve those scientific questions that address the alleviation of the greatest suffering? Given the increasing recognition that animals and plants and our ecosystem as a whole should not only be protected for the sake of human health and wellbeing, but also in their own right, how can we ensure that the interests of all species are considered in regulation and governance decisions?

There is a clear need for collective, inclusive, democratically legitimate ways to decide what new genome editing techniques should be used for in each area, as well as how such responsible use should be safely regulated.

Recommendations

On the basis of the manifold aspects and potential implications of genome editing in humans, animals and plants, including a particular attention to gene drives, outlined and ethically analysed in the chapters of the Opinion, and noting that the recommendations should not be seen as an endorsement of specific technologies, applications, or application areas, the EGE recommends to:

On overarching matters and concerns

- Foster broad and inclusive societal deliberation on genome editing in all fields of application and with a global scope;
- Avoid narrow conceptualisations to frame debates about the ethics and governance of genome editing;
- Develop international guidelines and strengthen national, regional and global governance tools;

On genome editing in humans

- Engage in global governance initiatives and create a platform for information sharing and inclusive debate on germline genome editing;
- Establish a public registry for research on germline genome editing;
- Protect social justice, diversity and equality;
- Ensure adequate competencies in expert bodies;

On genome editing in animals

- Strengthen oversight of genome editing in animals for scientific experiments according to, and beyond, the 3Rs;
- Apply strict standards to experimentation with non-human primates and invest in the development of alternatives;
- Broadly discuss the humanisation of animals and implement appropriate limitations;
- Regulate the banking and farmingon animals carrying human organs for transplantation;
- Prevent unregulated use of genome editing tools;
- Strengthen ethical oversight of practices involving reductions of animals' natural
- abilities;
- Ensure the wellbeing of genome edited livestock animals;
- Reconsider ethically contested industrial farming practices;

On genome editing in plants

- Carefully assess the potentials and risks of genome edited plants for agriculture;
- Develop an (eco)systems approach for evaluating the costs and benefits of genome edited crops;
- Develop mechanisms to ensure corporate responsibility;
- Investigate mechanisms for traceability and labelling of genome edited crops;

- Develop measures to support small actors;
- Devote more attention to public debates about genome edited agricultural products;

On gene drives

Acknowledge epistemic and other uncertainties;

- Use gene drives in ways that are based on shared values;
- Regulate, monitor after release and have mitigation plans in place;
- Retain stock of original organisms.

The European Group on Ethics in Science and New Technologies (EGE) is an independent, multi-disciplinary body appointed by the President of the European Commission, which advises on all aspects of Commission policies and legislation where ethical, societal and fundamental rights dimensions intersect with the development of science and new technologies.

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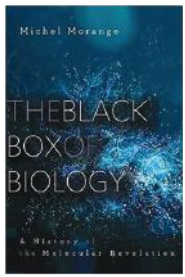
Book Review

The Black Box of Biology
A History of the Molecular Revolution



Author: Michel Morange
Translated by Matthew Cobb
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In October 2020, two scientists, Emmanuelle Charpentier and Jennifer Doudna were awarded Nobel Prize for the development of a gene manipulating method. The revolutionary 'Clustered, Regularly Interspaced, Short Palindromic Repeats' in association with the Cas9 DNA-cutting enzyme (CRISPR/Cas9 genetic scissors) is 'one of gene technology's sharpest tools for re-writing the code of life' (The Royal Academy of Sciences, 2020). Though its benefits are immense, CRISPR is seen as a 'double-edged sword' (Yang et. al., 2020; Zhu et. al., 2020). It is increasingly criticized for its limitations and potential risks. Scientists have raised numerous scientific, ethical, societal and governance issues associated with CRISPR (Shwartz, 2018; NAP, 2020). In the latter half of the last century, there has been tremendous incremental research and advancement in genetics. Amidst this, it will be interesting to unravel the origins and development of this field, and this book under review, published few months before the Nobel Prize was announced is very timely and takes us through the journey of the Molecular Revolution - opening the 'Black Box of Biology'. The book is comprehensive, written in a style that is understandable to general readers, who may not necessarily be scientists or biologists. It is well-written and simply translated. It succeeds the earlier version entitled 'A History of Molecular Biology' published in 1998, and was viewed as the 'definite and sophisticated account of review of molecular

biology' (Bynum, 1999). It gives fresh insights about the discoveries and development in biology during the last two decades and envisages its promises and risks in future.

The book has four parts. It derives its first three parts largely from the older edition however, there is an entirely new fourth section entitled 'Beyond Molecular Biology?'. The first part delves into the genesis of the science of Molecular Biology. The author begins by tracing the evolution and development of biochemistry in conjunction with advances made in related disciplines and sub-disciplines of science from the last decade of 19th century, and assesses and analyses various debates around theories and concepts like colloids, specificity, etc. including quantum mechanics. He then goes on to discuss the origins of genetics from second half of the 19th century, and it's essential role in the birth of molecular biology. The author tries to understand the growth of genetic research institutions in the United States and Britain in the context of greater realisation of its scope and application in agronomy. He highlights that the growth in genetic research was faster in US, where it emerged as a separate discipline, in contrast with European countries where it grew in association with other disciplines. Morange deals with the question - why isolation was necessary for development of genetics as a discipline?

Building on previous researches on mechanism of gene action and role of genes in development, author discusses the novelty of the 'one-gene-one-enzyme' hypothesis. It is viewed as the first step towards experimental association and the unification of biochemistry and genetics, and seen as the first major discovery of molecular biology. He asserts that the birth of molecular chemistry needs to be examined through its association with varied sciences like physics, mathematics, etc. The book gives an account of scientists involved and their research. In his endeavour, Morange gives an interesting peak into the challenges and issues faced in scientific research by the scientific community. He identifies concerns over the newness of the phenomena, which was against the widely held view and poor understanding of the structure and properties of nucleic acids, as main reasons for lack of recognition of the importance of American microbiologist, Oswald Avery's discovery. Though he notes that the revolutionary character of his experiment was not recognised at that time, but he held that it did open the door for future researchers.

Realising the significance of research groups, the author very aptly discusses the formation of an informal 'phage group' which used bacteriophages as a model to study reproduction in organisms. The most striking part of his discussion on the phage group was his emphasis on change in 'culture' within laboratories, which aimed to do away with hierarchies and provided scope for freedom of discussion and close mixture of work and pleasure – marking a change in the way laboratories functioned – and imitating a tradition of thinking about experiments. The role of phage group could be assessed through its psychological and cultural influence and their annual practical course. He also brings forth the contrast between a largely secluded isolate research undertaken by Avery where the researcher could not bring attention to his research with the influence and activity of the phage group network. Thus, underlining the importance of scientific networks and their role in furthering science which immensely benefited Hershey and Chase's experiment.

Laboratories are affected by socio-economic and political context too. Morange recognises this and blends his narrative with the socio-political and economic context of laboratories and circumstances faced by individual researchers/scientists. In the first half of the twentieth century, the study of bacterial physiology and experiments in bacterial genetics began. The author discusses collaborations between scientists and impact of political circumstances on scientists. Asserting role of physicists in the birth of molecular biology, he explains why physicists were increasingly interested in biological research – contextualising it within the post-world war period and scientists' role in war efforts. There is however a difference of opinion among historians regarding the nature and extent of their influence. Increasing specialisation of science today gives opportunity to very few physicists or mathematicians to propose new observations in biology. This is in sharp contrast with the situation in the first half of twentieth century when physics and chemistry bridged the gap in biological knowledge.

Funding institutions play a critical role in furthering scientific research. Recognising this, the author assesses the Rockefeller Foundation which according to him played a key role in the birth of the molecular biology by encouraging young scientists, equipping laboratories and developing high-ranking laboratories. He analyzes changing focus of their funding schemes after the Great Depression and scrutinizes their evaluation process which

significantly influenced the direction of research. At the same time, Morange also brings forth limitations of these grants and notes that the foundation did not fund many institutions that later played an important role and gave grants to relatively rich and well-known research groups – bringing to light the complexities of science policy and funding. He cites the example of the Institut de Biologie Physico-Chimique (IBPC) of Paris which was hit hard by socio-political issues during World War II. As a result, the Institut Pasteur was instrumental in development of research in molecular biology in France.

In the second part, author discusses the developments in Molecular Biology primarily the evolution of the double helix model, convoluted deciphering of the genetic code and the complexities of the discovery of the messenger RNA. Emphasising on the significance of collaborative research, Morange describes the story of Watson and Crick's collaboration and discovery. Apart from discussing various other models of DNA, he focuses on the role of women scientists like Rosalind Franklin, whose crystallographic data were important for the discovery of the double helix structure. He brings forth issues and challenges faced by women scientists in STEM fields and her hardships and lack of recognition in the laboratory. He specifically notes that her work could have earned her the Nobel Prize. These challenges are faced by women scientists even today, which result into lesser representation of women in STEM fields.

The discussion relating to the French school gives an understanding of the nature of French universities and the society. During the interwar period, developments of biochemistry was non-existent in France when compared with Germany, Britain and America. He observes that the reasons include rigidity and top-down culture in French universities and slow rate of formation of university chairs in genetics. Despite these handicaps, France played a significant role in advancement of molecular biology. The author emphasises on the scientific autonomy and independence provided by the Pasteur Institute. These unique favourable conditions at the institution provided an ecosystem for scientific research and development of international scientific networks of researchers. Besides this, the Nobel Prize in 1965 also had a major impact. The author very eloquently discusses the role of scientists like Jacob, Lwoff, and Monod in not just furthering French molecular research but also effecting the 'culture' in French universities and society at large. Thus, highlighting importance of scientists' freedom of/

in research and their role and ethical responsibility towards society, which had increasingly gained attention during the post Second World War era.

The author in the third part of the book takes the story ahead into the expansion of Molecular Biology through genetic engineering, gene splitting and splicing, discovery of oncogenes and amplification of genes, moving towards application of these new techniques. He describes the limitations in studying the history of technology and enumerates the technological network, new techniques which benefitted the origins of genetic engineering. Historians have difference of opinion regarding its origins. The genesis of genetic engineering according to Morange was marked by the experiment at Stanford, published in the *Proceedings of the National Academy of Sciences* in 1972. The development, techniques and applications of genetic engineering, gene splicing and splitting aroused numerous debates among scientists during the period. Various models explaining the development of cancer and history of emergence of oncogene paradigm, along with reasons of its wide acceptance has been discussed by the author. The discovery of the polymerase chain reaction, a technique to amply DNA has enormous benefits and application which earned it the Nobel Prize and was seen as a technique which changed the work of molecular biologists. Morange also brings forth Thomas Kuhn's concept of *Normal Science* in his discussion.

The last part of the book engages with the question of 'Beyond Molecular Biology?'. It focuses on the developments in the past two decades and explores the continuities that exists between these and the earlier developments. The section tries to understand the relevance of the mid-twentieth century frameworks for recent developments. It also delves into the interaction between various science fields and takes the readers through a journey of significant researches and developments in molecular biology. The chapters explore the continuities and change in study of molecular biology and related fields through developments like molecularisation of biology and medicine, advances in protein structure, changes in understanding of embryological biology (now known as developmental biology), relationship between molecular and evolutionary biology. It is interesting to read the discussion on CRISPR/Cas9 in gene therapy as one relates it with the developments at present. Morange notes the move away from Francis Crick's dogma, which recognized RNA as an intermediary and emphasises on its unique role as a fundamentally important molecule.

At the same time, he deals with epigenetics which shakes the classical foundations of molecular biology. The author also traces origins and key events of the Human Genome Project, Systems and Synthetic Biology. Though interests in latter developments have dissipated, physics assumes a far greater role in molecular biology. These developments have accentuated intense debates within the scientific community. The final chapter analyses images, metaphors and representations in molecular biology to gauge the transformation in portraying scientific discoveries and assess radical changes or continuities.

Through a historical analysis of the socio-economic-political scientific development of molecular biology, the author touches upon the intricacies of the progresses made and interaction between various scientific fields. The author opens the *Black Box of Biology* and delves into multiple-dimensional understanding of the transformation of biology. He succinctly puts forth that although the term molecular biology is rarely used now, has seen a decline in popularity and has been infiltrated by various disciplines – molecular biology remains integral to various recent developments and remains fundamentally important for biologists even today. The insights into 'culture' of science and impact of socio-economic and political context blends very well in the first two parts of the study, however it is not adequately dealt with in the last two parts. It would be interesting to see the recent developments through these lenses. The book notes the importance of representations and images, but lacks to include them to make it visually more engaging and illustrative. As the book gives an exhaustive account of scientists involved in the long history of molecular biology, a glossary of these scientists with short biographies at the end of the book would have been useful and interesting for the readers.

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Book Review

Ethical Tensions from New Technology: The Case of Agricultural Biotechnology

Edited by: Harvey S. James, Jr.
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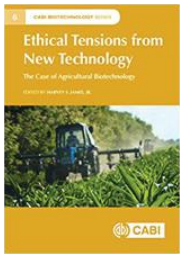
Year: 2018



In India, in the month of May, 2019 the leaking of genetically modified Brinjal into a farmer's field in Haryana led to uprooting the entire field to remove the traces of it (Bera, 2019), depicting a typical case of indecisiveness of policy makers with the available genetically modified (GM) crops and the uncertainty associated with the technology. The indecisiveness is due to ethical tensions that arise from differences in interests, values, power and rights among the different stakeholders. This book edited by Harvey James Jr. explores the ethical tensions that agricultural biotechnology and GM food creates by arguing the benefits of agricultural biotechnology to improve food system while advancing the interests of humans, animals and the environment and at the same time raising the ethical concerns without being blinded by the assumption of inherent efficiency of technological innovation.

This volume, a collection of twelve essays, is a compendious statement of ethical questions that creates 'fault lines and pressure points' with respect to new technologies particularly agricultural biotechnology and GM food. The essays have mainly addressed four domains - public opinion and public interests; policy and regulation; relationship between new technologies and the social, economic or environmental problems; and interaction between new and old technologies, in an attempt to ameliorate the ethical tensions and to use agricultural biotechnology to improve food and food systems.

In the first section, four essays - *Ethical Tensions from a Science Alone Approach in Communicating Genetic Engineering Science to Consumers* by Kolodinsky; *Against the (GM) Grain: Ethical Tensions and*

Agrobiotechnology Activism in the USA by Jones; *The Use and Abuse of the Term 'GMO' in the 'Common Weal Rhetoric' Against the Application of Modern Biotechnology in Agriculture* by Areni; and *Collaborating with the Enemy? A View from Down Under on GM Research Partnerships* by Ankeny, Bray and McKinley focuses on ethical tensions relating to GM food which governs 'public opinion and interests'.

Kolodinsky's chapter raises the issue of non-alignment between science and communication which leads to ethical tensions over the use of agricultural biotechnology. She argues that 'science alone approach in communicating' has failed to address the fundamental concerns of the public when viewed against 'the ethical principles of autonomy, non-maleficence, beneficence and justice'. As a result ethical tensions would remain at the public level and facilitating science communication (with consumers) can buffer the debate. In the following chapter, Jones presents two cases of public-political mobilisation around the GM food in USA: Occupy The Farm and March Against Monsanto, which raises the issue of 'bioinsecurity' among the mass – where the perceived threat is not just from the altered organisms but the system responsible for studying threats has been compromised. The essay by Areni on the other hand, focuses on the motives, agendas and 'opportunistic behavior' of the opponents of GMOs which creates ethical tension between their interest in influencing political opinions and the actual interests of the general public. The author terms the obvious criticism for GMOs as 'common weal rhetoric' advocated by anti-GMO cadres to position themselves as voices of the public interest. The author also ascribes the regulatory response of the European Commission to make the complex social and environmental problems with respect to agricultural biotechnology appear as a simple dichotomy of 'people versus profit', and branding anything involving GM technology as 'bad'. Areni presented two cases - 'the National Research Program launched by Swiss Federal Council' and 'the Heubuch Report of the EU Parliamentary Commission on Development', to support that 'common weal rhetoric' does not always advance public interest. The funding patterns and public-private partnerships in the development of GM crop types in Australia has been presented in the fourth essay, where the author describes that there exists no direct correlation between private interests and research funding

for agricultural biotechnology. The authors analysed the applications to the Australian regulatory authority for intentional release of GMOs to determine the alignment of research funding, which showed research funds for GMOs well-aligned to the public needs and benefits, in order to reduce environmental impacts and growth of crops in extreme climatic conditions.

The second section on 'Policy and Regulation' consists of three chapters. The first chapter by Duane Windsor addresses a normative question of whether pro-GMO science and business should lead or follow public opinion. The answer is, it varies. Since, scientific facts around GMOs are uncertain and welfare of human beings from GMO agricultural products are yet to be established, different ethical positions of 'precaution, conventionalism and accommodation' operates across different nations globally. The author presents three models of precautionary (public policy is hostile to GMOs, where public opinion leads and biotechnology research follows as evident in European regulatory system), conventional (public policy is favourable to domestic agriculture, where public opinion is preferred over GE experts as evident in agricultural countries) and accommodative (public policy is favorable to GMOs, where agricultural biotechnology leads and public opinion neutral, as evident in US regulatory system) to explain how public opinion is linked to regulatory approaches and how it varies. The chapter by D.M Strauss calls for a mandatory clear and comprehensive labeling that discloses genetically engineered ingredients for an informed consumer choice. To address the ethical tensions relating to informed consent, she proposes a framework which embraces 'all stakeholders like farmers, consumers, the environment, underprivileged populations and the agricultural biotechnology industry' in policy development. Kolady and Srivastava in their chapter, demonstrated a comparative analysis of the regulatory systems in the USA and India to determine how ethical tensions regarding the regulation of agriculture biotechnology arise and how institutional framework, domestic politics address these in regulatory policy outcomes. In India, science academies remain limited in providing inputs toward policy and are more restricted functionally than the S&T academies in the USA. This became clear when the science academies for the first time in 2010 were requested by Union Government to conduct a joint academy evaluation and provide scientific advice on the release of

genetically modified Brinjal (Bt Brinjal), while the National Academy of Science of the USA offer scientific and technological inputs on several issues related to public policy on a regular basis (Menon and Siddharthan, 2015). The authors stated that unlike USA, 'the heterogeneity of stakeholders and the diversity of prevalent ethical concerns coupled with the influence of domestic politics make the regulatory process in India complex and uncertain' (p.109). As a result, despite the recommendation of the scientific body to commercialise Bt Brinjal, the Minister of Environment, Forests & Climate Change in India imposed a moratorium on its commercialisation. The authors also point to the disconnect between science and society in India, which hinder regulatory agencies to make science-based decisions. Institutions which goes beyond top-down communication to engage with the public for an inclusive and egalitarian advancements of S&T can provide indicators for a greater science-society interaction and for a robust ethical framework (Chaturvedi and Srinivas, 2013).

The two chapters '*Technological Pragmatism: Navigating the Ethical Tensions Created by Agricultural Biotechnology'* by Scott and *'Absolute Hogwash: Assemblage and the New Breed of Animal Biotechnology'* by MacDonald in the third section addresses with 'technological fix criticism'. Scott describes the optimistic and pessimistic perspectives relating to agricultural biotechnology and their associated ethical tensions. To avoid the polarized ideological trap and ethically ambiguous nature of new agricultural biotechnologies, he sets forth the adoption of philosophy of technological pragmatism which is capable of 'providing the conceptual tools to navigate the thicket of ethical tensions created by agricultural biotechnology' (p. 119). MacDonald also raises the issue of ethical tensions in the agricultural food and animal production by using the example of 'Enviropig'. Enviropigs are genetically engineered pigs which were produced by inserting a gene from a mouse to digest phosphorus in its food supply and to reduce phosphorus in the pig excreta. The author stresses that since animal based food production system (both intensive animal production without biotechnology and GE animal) are contentious in themselves, the ethical tensions arising out of it forces us 'to face the realities of our productivist food system' and not the engineering technology to solve one aspect of it.

In the fourth section 'new versus old technology' is echoed in the ethical dilemma governing CRISPR (clustered regularly interspaced short

palindromic repeats) genome editing technology (by Pirscher, Bartkowski, Theesfeld and Timaeus) and cognitive challenges for innovators with respect to new technologies (by Ng and James Jr.). Pirscher *et al*. argued that the development of new technology like CRISPR/Cas has induced a debate on the adequacy of the current governance system (within the European Union) due to the current non-traceability of the CRISPR/Cas generated modifications (CRISPR/Cas does not leave detectable traces of foreign DNA snippets in the modified organism so they are called nature-identical genetically modified organisms and cannot be identified as GMOs), as compared to the former genetic modification techniques. Hence, their regulation too focus on the process by which genetic modifications occur rather than the final product, giving rise to a new set of ethical tensions different from those arising out of GM crops. Also, since 'CRISPR/Cas technology is easy to apply, cheaper and much quicker', its outreach could be immense therefore, its governance need a continuous discourse between science and society. Ng and James Jr. in their chapter have tried to convince the readers that 'entrepreneurs not only face an ethical tension between the interests of stakeholders and the interests of society, but also can lapse in their ethical obligations to their stakeholders'. Using the case of a novel technology- CRISPR/Cas, they argue that the complexity and novelty in the decision-making process to commercialise such technology can lead to biases of the innovator to anticipate all the ethical implications on indirect stakeholders. They conclude by stating that 'if the introduction of new technologies, such as CRISPR/Cas9, is intended to advance the interests of all stakeholders, then decision makers need to be particularly vigilant in ensuring that indirect stakeholders are given appropriate ethical consideration' (p.159).

The fifth and last section contains one chapter '*New Technology, Ethical Tensions and the Mediating Role of Translational Research*' by Valdivia, James, Jr. and Quiroz where the authors suggests the use of translational research methods for decisions regarding adoption of new technologies and to ameliorate some of the ethical tensions arising out of the new technologies. This is because translational research facilitates two-way communication among relevant stakeholders (say scientists and farming communities). Translational research is a multidirectional and multidisciplinary integration of basic research with the aim 'to enhance the

adoption of best practices in the community' (Rubio *et al*, 2010). The success of translational research methods lies in the flexibility to accommodate the needs of individual institutions, so that it can effectively mitigate the concerns of the stakeholders and conflicts arising from new technologies.

There is thematic coherence in the organisation of the volume and in recognising the ethical tensions arising from the introduction of a new technology. Individual authors in each chapters addressed the issues of ethical conflicts and how to reconcile with them by developing an overarching regulatory framework governing new technologies and shaping the development policies.

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