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“O brave new world” CRISPR Mediated Gene Editing in Somatic and Germ Line Contexts for Therapeutics and Enhancement of the Human Species – an Ethical and Legal Discussion.

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RCSI

"O brave new world"

CRISPR Mediated Gene Editing in Somatic and Germ Line Contexts for Therapeutics and Enhancement of the Human Species – an Ethical and Legal Discussion.

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A dissertation submitted in partial fulfilment of the requirement for the Masters in Healthcare Ethics and Law

Supervisor: Dr. Siobhán O'Sullivan

August 2016

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I declare that this thesis, which I submit to RCSI for examination in consideration of the award of a higher degree, MSc in Healthcare Ethics and Law, is my own personal effort. Where any of the content presented is the result of input or data from a related collaborative research programme this is duly acknowledged in the text such that it is possible to ascertain how much of the work is my own. I have not already obtained a degree in RCSI or elsewhere on the basis of this work. Furthermore, I took reasonable care to ensure that the work is original, and, to the best of my knowledge, does not breach copyright law, and has not been taken from other sources except where such work has been cited and acknowledged within the text.

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Abbreviations

ADHD – Attention Deficit Hyperactivity Disorder

APD – Antisocial Personality Disorder

BMA – British Medical Association

CD – Conduct Disorder

CRISPR - Clustered Regularly Interspaced Short Palindromic Repeats

DNA – Deoxyribonucleic Acid

DSB – Double Stranded Break

EU – European Union

HBB – Human Beta Globin Gene

HDR – Homology Directed Repair

HFEA – Human Fertilization and Embryology Authority

MP – Member of Parliament

NHEJ – Non-Homologous End Joining

OCT – Ornithine Transcarbamoylase

PGD – Pre-Genetic Diagnosis

TALEN – Transcriptional Activator Like Effector Nucleases

UK – United Kingdom

UNESCO – United Nations Educational, Scientific, and Cultural Organisation

UV – Ultra Violet

ZFN – Zinc Finger Nuclease

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Abstract

Gene editing has been a topic of controversy since the late 1970's, however as of 2015 the topic of gene editing and its potential applications has shot to the forefront of biomedical ethical and legal debate. CRISPR is a new molecular technology, which is essentially a molecular scissors capable of cutting a single gene, or multiple genes out of the genome of any species. Scientists have manipulated CRISPR so that after it has excised a gene, or genes, it can then insert a gene of choice, selected by scientists, into the excised area. The ramifications of CRISPR mediated gene editing technology are huge in the cellular therapeutics arena (somatic), and in the preventative medicine landscape (germ line). CRISPR mediated gene editing requires us to reflect on how as a society we view genetically driven diseases, and disabilities. Furthermore, there are calls from scientists to clarify the legal and regulatory landscape of gene editing, in all its platforms, within their jurisdiction. In this piece, I examine the ethical and legal implications of CRISPR mediated gene editing in somatic and germ line contexts, using the British Medical Associations Eclectic Method.

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1. Introduction

1.1 History of Gene Editing

The human genome comprises of hundreds of genes[1], which act together as part of a network to confer functionality to a species. Gene's are our most tangible correlates to who we are as an individual, a member of a family, a race, and a species. Naturally, endeavours seeking to explore genes, the most fundamental units of a human being, will arouse public debate. Moreover, exploring techniques that seek to harness, manipulate, or alter genes will attract greater public interest, inquiry, and opinion.

Gene editing, also referred to as "genetic engineering", "genetic modification", "gene therapy", or "gene surgery", has, in some form, been in existence for thousands of years. For years humans have brought about genetic changes in, for example; canine species through selective breeding. Evidently, humans have always had a sense of what gene editing is through their experiences of breeding livestock, and crops, albeit a different understanding to what the term means today. The term gene editing changed in meaning to what we commonly understand the term to mean today, with the advent of viral vector systems in the 1970's. The paradigm shift in gene editing is illustrated in Jaenisch and Mintz (1974) where viral DNA was successfully incorporated into developing mouse embryos *in vitro*. The study highlighted that it was possible to take

[1] A gene is made up of DNA and is the basic physical and functional unit of hereditary. Genes act as instructions to produce proteins, both structural and metabolic.

DNA from one species and incorporate it into another. Henceforth, public opinion, and some scientific opinion were fearful of gene editing. In his letter Berg (1974) stated how experiments involving gene editing, particularly those involving the creation of gene edited bacteria, should not be performed:

"…our concern for the possible unfortunate consequences of indiscriminate application of these techniques motivates us to urge all scientists' working in this area to join us in agreeing not to initiate experiments…"

Almost forty years ago, while the scientific community focused on the potential harms of gene editing principally regarding the introduction of new pathogenic species into society, the public discourse was much more animated. The "Frankenstein factor" described by Gaylin (1977) neatly conveys the public's apprehension to gene editing. As noted earlier, genes are our most tangible correlates to our humanity, and now a small minority of people, the Dr. Frankenstein's, commanded a technology that could potentially edit genes, and thus manipulate humanity. Gene editing, therefore, conjured images of monsters and strange new life forms among the public. Both the public and scientific furore settled down once the technical complications and challenges involved in viral vector gene editing were realized. Viral vector methods instead proved more useful as a biological tool for studying gene function, disease modelling, and cell signalling processes.

1.2 Gene Editing Technologies

1.2.1 ZFNs and TALENs

Presently, the gene-editing furore has been re-ignited with the introduction of techniques utilizing a system based on endonucleases[2]. What was conceptual in the late 20th century is fast becoming a reality with the use of endonucleases. There are three main endonucleases, the first two; Zinc Finger Nuclease's (ZFNs), and Transcriptional Activator Like Effector Nucleases (TALENs) were the first endonuclease methods to be discovered, and applied to the genomes of multiple species, most notably humans. The advantage of these two methods, over the viral vectors previously described, is that they are exceedingly more specific and sensitive. However, ZFNs and TALENs are not without their faults, high cost, the size of the molecular editing system, the number of unintended off-target mutations, and the laborious process involved in their creation, make ZFNs and TALENs challenging to implement on a wide research scale, Ledford (2015a).

1.2.2 CRISPR

While scientists are still refining CRISPR-Cas9 (hereafter referred to as CRISPR), it has surpassed ZFNs and TALENs, given it's: low cost, high sensitivity and specificity, and capacity to target multiple genes simultaneously. Given these advantages, fear and unrest began to ripple through the scientific community in early 2015 when it was

[2] Endonucleases are enzymes (a type of protein) that can cut DNA at specific points.

speculated that some research groups might have been implementing CRISPR in studies involving human embryos. Unlike in the somatic cell context, editing the germ line of human embryos meant that any edit introduced to the germ line could potentially be passed on to future generations. The unrest led to calls for a specific moratorium on germ line gene editing research. Indeed this fear was well founded as Liang, Xu et al. (2015) published a research article in which they used CRISPR to gene edit the germline of human embryos.

1.3 The Present Day Gene Editing Landscape

Gene editing methods before CRISPR would not have been reliable, sensitive, or specific enough to carry out molecular work at the germ line level. Crucially, however, regardless of ethical and legal status, CRISPR can be readily implemented by both scientists and non-scientists, with reasonable efficiency and at a low cost, something that has not been possible in gene editing prior to CRISPR's discovery. Understandably, CRISPR's accessibility and utility inflames debate regarding who has access to it, and how it should be used.

Liang's (2015) paper broke effectively broke a 40-year moratorium on human germ line gene editing. Breaking this moratorium, and introducing a technology as powerful as CRISPR, has now forced us to question how this technology should be harnessed. CRISPR has the potential to be truly beneficent in how it changes the

medical landscape through gene edited somatic cell therapies, however much of CRISPR's maleficence lies in it's capability to alter the genetic structure of the germline of developing embryos. Subsequently, genes associated with human impairment, could be edited out of the human species. Furthermore, discourse has begun to stray from using gene editing to "treat" genetically based impairments, to a discourse regarding enhancing humans by removing, inserting, up or down regulating certain genes. Naturally, as with any other medical intervention, concerns regarding the autonomy of the individual undergoing the procedure, or in the case of germ line edits, the autonomy of the individual consenting to the editing of an embryo, are pulled into focus.

A striking similarity, however, between gene editing of the 1970's and today's gene editing domain, is the lack of regulation regarding the criteria, and context for using gene-editing techniques at either a somatic or germ line level. Most countries have banned editing the germ line of human embryos, but allow for editing of human somatic cells. Meanwhile other countries choose not to abide by the moratorium, as was the case in China through the publishing of Liang's (2015) paper. Governance and regulation for gene editing techniques will be fraught with moral, ethical, and philosophical quandaries that will be societally specific. Effective regulation of CRISPR will require international co-operation, as well as significant national discourse.

1.4 Aims

It is my aim through the course of this thesis to implement the British Medical Associations (BMA) Eclectic Method to understand the controversy surrounding the use of CRISPR gene editing technology to edit human genes. Implementing the BMA Eclectic Method in relation to CRISPR mediated gene editing requires an analysis of; (i) clinical evidence, (ii) community values (iii) ethics, and (iv) law. The chapters of this thesis will follow the name and order of the above categories.

2. Clinical Evidence

2.1 The Science of Gene Editing

Gene editing was conceptualized in the 1970's, and first implemented in the 1980's writes Church (2015). The reason gene editing has become such a contentious point of debate in society is that, now gene editing methods such as CRISPR, and to some extent it's fellow endonucleases ZFN's, and TALEN's, are synonymous with germline editing. Currently, gene editing clinical trials are numerous, most of which do not involve the endonuclease methods listed above, a selection of these trials are detailed in Naldini's (2015) paper. Naldini refers to gene editing involving vectors[3], which have been designed to edit genes associated with, for example, haemophilia, βeta-thalassemia, and B cell lymphoma. Notwithstanding the advancements being made in "non-endonuclease gene editing techniques" the specificity and sensitivity of endonuclease methods have become much more appealing to researchers.

Endonuclease gene editing techniques all function with a similar principle: a nuclease is guided towards a pre-selected target DNA sequence and induces a double stranded break (DSB). There are many agents (mutagens) that can bring about DNA breaks, e.g. UV light, and in order for the cell to continue functioning the cell must either repair the break or undergo programmed cell death via apoptosis. In the case of

[3] Vector: is a multifunctional synthetic structure designed to incorporate gene sequences or deliver a biological construct into a cell.

repair the DSB can be repaired by one of two pathways; non-homologous end joining (NHEJ) or by homology directed repair (HDR), see figure 1.

The endonuclease techniques take advantage of the aforementioned repair pathways. Instead of a natural mutagen inducing a DSB, an endonuclease system can be designed by researches to break the DNA at a target gene sequence. Researchers wanting to remove (knock-out) a gene can use an endonuclease to cleave a specific sequence of DNA causing the cell to undergo NHEJ. The flanking regions of the cleaved gene are joined together, thus removing functionality of the gene. Conversely, a gene can be added (knocked-in) via the HDR pathway, where a homologous exogenous donor DNA template[4] is added to the cell once the DSB has occurred, resulting in the uptake of a new gene sequence, see figure 2.

ZFN's and TALEN's are effective gene editing methods; however they are laborious to create and implement, which in turn drives up their cost. Moreover studies have shown that while effective in cleaving a target gene, there are multiple off-target anomalies. The introduction of CRISPR to the field of genome editing provides a system that is, by comparison, cheap, easy to use and apply, and reduces the degree off-target effects. CRISPR genome editing has three primary applications clinically:

[4] This template is designed in the laboratory and delivered into the cell alongside the CRISPR construct. The template contains a gene to be added which will correct for the function of the gene that has been removed. Or, the template may contain an entirely new gene to replace the removed gene, and alter the cells function entirely.

(i) Somatic Non-Clinical: as a method and platform to conduct research into cellular signalling pathways and disease models.

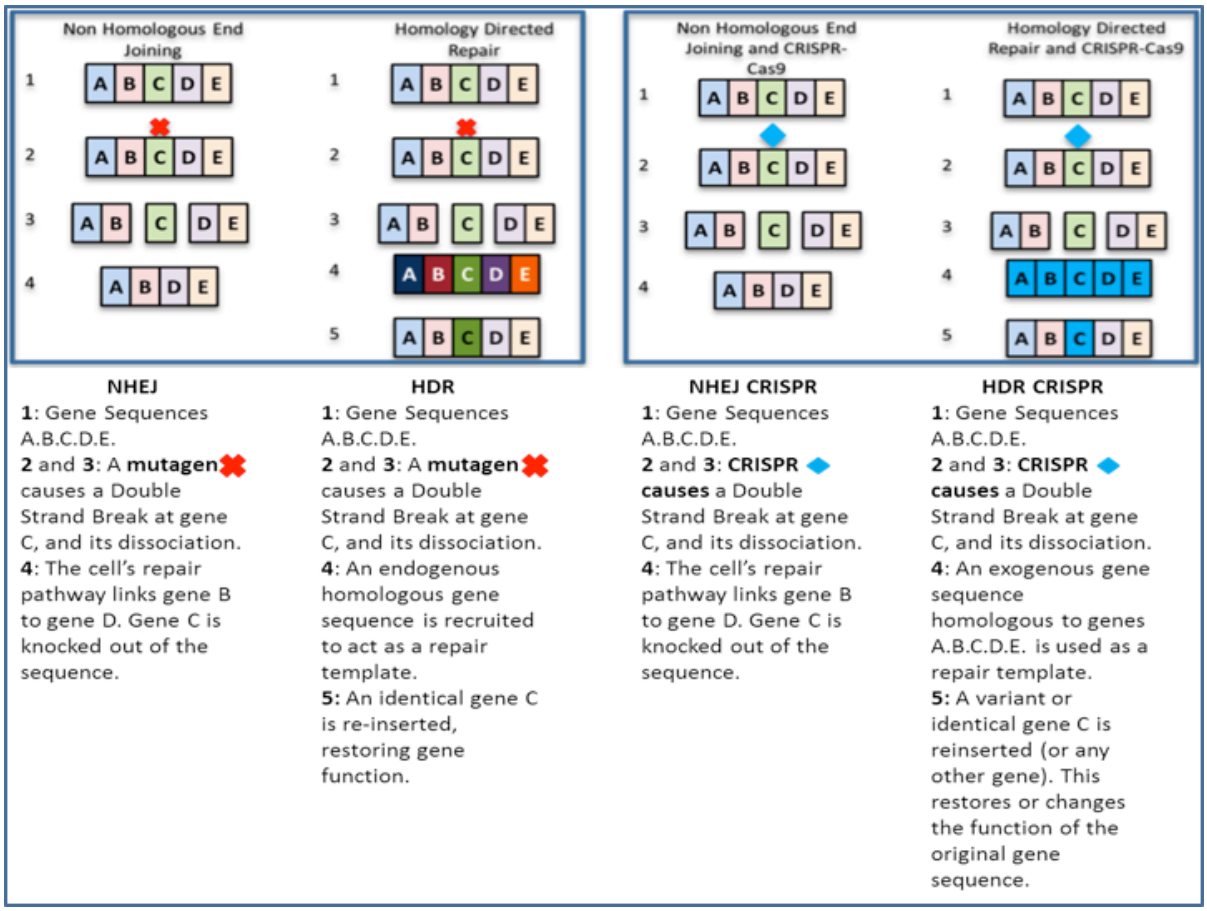
(ii) Somatic Clinical: as a tool to assist in the realization of emerging regenerative medicine therapies.

(iii) Germ Line Clinical: as a method to alter the human genome in order to edit out, insert, or repair genes of disease or to manipulate the genome to up-regulate or down-regulate genes that confer specific or desirable phenotypes.

The applications of points one and two, listed above, are associated with human somatic cells, while point three is associated with editing the human germline.

Figure 1: Cellular Repair Pathways for a Mutagen Induced Double Stranded Break (Adapted from Maxmen 2015)

Figure 2: How CRISPR Uses Cell Repair Pathways to Remove or Add Gene Sequences (Adapted from Maxmen 2015)



2.2 Clinical Evidence for the Somatic Non-Clinical Platform

Jinek, et al. (2013) was the first to describe the CRISPR platform most commonly used today. In Mali's (2013) study CRISPR was shown to induce repair in human embryonic kidney cells. Researches can extrapolate from this study, that it is plausible to manipulate genes in a manner that affects cells functionality; meaning key cell signalling pathways and events can be analysed in a stepwise manner, based on gene function.

CRISPR allows researchers to alter a cells genome to suit a specific disease genotype in its purest form. Whereas inducing the gene profile of interest *in vitro* allows researchers to study the effects of the induced genotype in isolation. Choi (2014), for example, studied the role of multiple chromosomal rearrangements and inversion profiles seen in patients with lung adenocarcinoma, using CRISPR, thereby opening the door for highly sensitive and specific drug susceptibility models.

2.3 Clinical Evidence for the Clinical Somatic Platform

Currently, regenerative medicine is a source of exciting new therapies, whereby the goal of the medical intervention is not to treat with an aim of elevating symptoms, but instead to restore function to a defect biological system. Schwank, et al. (2013)

studied the functional repair of the CFTR gene in intestinal stem cell organoids[5] derived from intestinal cells of patients with Cystic Fibrosis. Schwank showed that it is possible to correct the human CFTR gene using a CRISPR construct and thereafter develop an intestinal organoid. Although transplantation of the developed CFTR corrected organoid did not occur, Schwank states that, in line with previous studies in which transplantation of a corrected organoid has occurred, the current results provide a potential strategy for gene therapies.

Research conducted by Yin, et al. (2014) provides evidence in relation to correcting a disease *in vivo*, with a cellular therapy designed *in vitro*. Yin, studied the role of the *Fah* mutation in murine hepatocytes, which is responsible for the development of hereditary tyrosinemia – a fatal genetic disease. Interestingly the mutation seen in the murine *Fah* gene is the same for human models of hereditary tyrosinemia. The research group showed that using a CRISPR construct to correct the point mutation was a viable way of restoring liver function in mice. Furthermore, liver function was restored when as little as 1/250 liver cells were corrected, highlighting the effect of positive selection in an organ construct. The author goes onto state that the study conducted was a "proof of principle study" that envisaged a clinical setting whereby diseases could be corrected *in vivo*, particularly those diseases where positive selection of a low number of corrected cells is enough to restore function.

[5] A 3D organ bud grown *in vitro.*

2.4 Clinical Evidence for the Clinical Germline Platform

While the aforementioned research in somatic cells involves the manipulation of the genome, it is done so in a manner that is non-transferable given the cell populations the therapy targets. Editing the germline of any organism will cause the proliferation of the edited gene into every cell of said organism, including the sperm of males, and ova of females. Not only will the edited gene be present in the organism that underwent the germline editing, but also should that same organism procreate, the edited gene will be passed onto the resulting progeny.

A murine model in which the gene responsible for Duchene Muscular Dystrophy was edited out of murine germline DNA using a CRISPR construct as was described by Long, et al. (2014). Developing murine zygotes[6] were edited using CRISPR and then implanted into pseudopregnant female mice – all mouse progeny developed into adults with no signs of tumour growth or abnormal phenotypes. The author states that CRISPR mediated genome editing is capable of editing and correcting a genetic lesion such as Duchene Muscular Dystrophy in their murine model, but also notes that correcting the same abnormality in a human model will take significant advances in medical research using CRISPR technology.

[6] A zygote is a cell that is essentially is the starting point of an embryo's development.

Notwithstanding the technical difficulties described in Long et al, a study conducted by Liang, et al. (2015) broke an international moratorium on germline gene editing by publishing a paper entitled "CRISPR-Cas9 - mediated gene editing in human tripronuclear zygotes." The research group set out to edit the human βeta-globin gene (HBB) in order to assess the specificity and fidelity of the CRISPR system in human embryos. The embryos used, were retrieved from a fertility clinic with patient consent[7] but had an abnormal chromosomal content and were not viable. Out of the 86 embryos injected by the research team for the correction of the HBB gene: 71 embryos survived, 54 were suitable for genetic testing, 28 were successfully spliced, 4 were edited with the exogenous DNA template, and 7 were recombined with an endogenous DNA template. Furthermore the study was plagued with off-target mutations even though only a select few genomic locations were analysed by the team. Had whole genome sequencing been applied, the author suggests that, many more mutations would have been identified.

As shown by the clinical evidence, the applications of CRISPR are far reaching. Not only does CRISPR allow researchers to elicit gene editing in somatic cells of multiple species, but it also enables editing of the human germline. While the results from Liang's germline editing study were juvenile and plagued with off-target mutations, I would argue that the study acts as a proof of principle. Today, there is the ability to at least manipulate the genome of developing embryos, irrespective of

[7] The research article does not give explicit information as to how patient consent was retrieved.

specificity, and that is cause enough to engage debate surrounding the inevitability of a manipulated, altered, or edited form of human.

3. Community Values

3.1 Overview of Human Health and Impairment

An individual is deemed healthy, if their biology is in accordance with our theories of health. The concept of "health" is an obscure one as it is based on an individual's, or a society's normative judgments of how a healthy person looks and how they function. Health, it is argued, should be studied in a phenomenological manner whereby ones experience of being at home in ones lived body is seen as being healthy rather than the mere normal functioning of their organs as a biological unit. Carel (2012) states that it is absurd to ask a person if they are healthy, as health by Carel's definition is the experience of being involved in the world, and participating in rewarding engagements. Similarly, Gadamer (1996) explains his theory of health as a person who is in harmony with their natural and social environs. However, by far the more commonly referenced definition of health, is that provided by the World Health Organisation (WHO 1948):

"Health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity."

Given the discourse and debate surrounding how best to describe the concept of health, it is with added complexity that the discussion of human impairment, which encompasses the concepts of disease and disability, is described. Physical and mental impairments of the human body incorporate a vast range of conditions, some of which may be genetically rooted. Impairment can be described as having reduced ability, or an inability to conform to a medical or social norm. In order to understand impairment, the concepts of disease and disability need to be explored through the lenses of two key philosophical standpoints, namely (i) naturalism and (ii) constructivism, and studied in relation to the aforementioned norms.

3.2 Naturalist Philosophy

Naturalist philosophy states that the body comprises of organ systems with normal functions that can depart in many ways, some of which may be harmless, however other paths of deviation may prove harmful. These harmful departures are, what naturalist's term, diseases. Whether an individual is diseased or not is a straightforward matter for a naturalist, given that once the malfunction is identified, the person is automatically classed as diseased. This account of naturalism is rather blunt; hence it is termed "simple naturalism" (Boorse, 1975). Building from simple naturalism, Boorse (1977) proposed his take on naturalism, whereby there are two key components to defining disease: (i) the malfunction must interfere with the performance of a normal function, and (ii) the malfunction should not just simply be in

the nature of the species. Expanding from these components, it is understood that by interfering with a human's performance decreases their chances of survival and reproductive capacity, secondly regarding the nature of the malfunction it is understood that some diseases are statistically normal, e.g. dental decay.

Boorse's theory creates a need to relativize the malfunction, and he achieved this using reference ranges that account for the age, sex, and race of the human undergoing testing. Aspects of Boorsian theory are still prevalent in parts of modern medicine, most notably laboratory medicine. Laboratory medicine relies heavily on the use of references ranges, for example analysing blood components. Unfortunately, flaws in Boorse's theory began to appear, as with the introduction of reference ranges came the requirement to make a distinction between a diseased state and an ill state. According to Boorse illness was described as: "undesirable to the bearer", "a valid excuse for normally criticisable behaviour", and "are a title to special treatment." Boorse's definition of illness relies heavily on normative judgments, which deviate from the empirical naturalist path. An exemplary case that highlights a flaw in Boorse theory is Boorse's response to classing homosexuality as a disease, as it decreases the reproductive capacity of the individual and is not statistically normal. Boorse accepts that homosexuality is a disease by his theory but, more importantly, stresses that homosexuality is not an illness, as it is not seen as something undesirable. In essence, a disease according to Boorse is a failure to conform to a species typical design, whereas illness is a matter of judgments seen to be unwanted or undesirable.

Critics of Boorse theory were quick to highlight that references ranges cannot be established without normative judgments. Notably, Kingma (2007) points out that organs can act in a situational appropriate way, which may not be healthy, but simultaneously are not diseases[8]. Murphy (2006), in my opinion, provides a neat naturalist construct for us to analyse disease. Murphy describes a two-tier naturalist approach, which sequesters aspects of the constructivist philosophy. First, an agreement is reached regarding the biological underpinnings of specific malfunction. Secondly, we make a normative judgment that the person harbouring the malfunction is suffering in some way. Ergo, we make judgments about people's suffering in ways that can be ascribed to inner malfunctions. Two-tier naturalist philosophy is designed to distinguish between the physical abnormality and the impact that abnormality has on ones quality of life. This attention to suffering is omitted in simple naturalism.

3.3 Constructivist Philosophy

Constructivist philosophy views impairments through the lens of value judgments. Constructivism states that it is up to a society to deem what is a diseased state and what is not, meaning that a disease must be something that violates our

[8] The liver may be impaired by a paracetemol overdose that will affect its overall function while trying handle the insulting overdose. The liver in this situation is acting in an appropriate way given the circumstances, however its normal function is impaired which by Boorse's theory, would make it momentarily diseased.

convention of health[9]. Constructivism gives a great deal of power to social judgments without due regard for an empirical biological opinion, furthermore Reznek (1987) states that a biological malfunction is not "a necessary condition" to label someone as having a disease. For constructivists the symptoms of a person are judged unusual because they depart from societal norms, meaning that diseases are harms that we blame on a biological process because it causes harm, not because it is inherently dysfunctional. Constructivist logic criticizes naturalist philosophy as it states that our search for causal biological facts only occurs in the wake of a disvaluing a particular trait exhibited by a person, hence leading the search for biological evidence to support the medicalization of that trait. These traits can include such things as alcoholism, and obesity.

Impairment has never been the only way for a person to deviate within society, however we routinely judge people to be less well off, and impaired without classifying them as diseased, such people include but are not limited to alcoholic people, poor people, homeless people, and ugly people. However, we do not treat these impairments, which are comparatively disadvantageous as a prelude to medical inquiry (Savulescu and Kahane, 2007). To be diseased in a constructivist framework requires that the person be worse off in a health related or medically specific way. Difficulties

[9] Anecdotally, constructivism can be compared to looking at works of art. Constructivists would look at a piece of art, and ask, "if it is art, how do we know?" Constructivists would then go on to clarify that art is not a fact in the world to be discovered, rather it is determined by society what is and is not art. For example most people would say that because a painting is exhibited in a museum, it is therefore art. Similarly, because a patient is treated in hospital, they by association are diseased.

with constructivism are encountered here, as now constructivists must try to explain why the value judgments directed at supposed "health impaired" people are of a special class.

Arguably, constructivism in psychology is the sole medical arena in which constructivism holds more sway over naturalism. Constructivist theory into psychological matters seeks to investigate how human beings create psychological systems from which they gain meaningful understanding of their world and experiences. Babli (2008) a proponent of constructivism in psychology states:

> *"The mind is conceived as a passive system that gathers its contents from its environment and through the act of knowing, produces a copy of the order of reality."*

While there may be a biological underpinning for a particular type or severity of psychological condition, the constructivist will instead focus on how the person is able to interact with their reality and the reality of others.

3.4 Disability Models

Considering the differences in the philosophies used to understand the concept of disease, it is equally as important to understand definitions of disability. Similar to disease, disability is based on the classification of people *vis a vis* traits that are observed or inferred. As with disease, it is particularly difficult to understand or to

classify disability from either a biological or social view. Coupling disability with the term inability or a limited ability only confuses the situation as it acts as an umbrella term for a vast range of diverse conditions, e.g. progressive neurological conditions, losses of limbs, and infections with viruses such as HIV. Two common disability constructs are (i) the medical model, and (ii) the social model. The medical model understands disability and the limitations faced by disabled people resulting solely from their biological impairment. In stark contrast, the social model understands disability and the associated limitations as being a result of the relationship between the person and their environment.

The medical model of disability is rarely defended as it fails to take into the account the rather obvious social barriers faced by people with disabilities; moreover the medical model appears to support the correction of the offending biological process. Whereas, the social model views the extent of a person's disability being highly dependent on their well-being, which is subject to social and environmental obstacles faced by the person with a disability.

A third model for the defining of disability is termed the "human variation model" (Scotch and Schriner 1997). This model views disability as:

"An extension of the variability in physical and mental attributes beyond the present – but not the potential – ability of social institutions to routinely respond"

Here, a universal view of disability is described, noting that there is a spectrum of human variation and under certain circumstances this variation may be deemed as a disability. The human variation model understands that at some time in any person's life they will acquire familiar impairments that we deem, in that time and circumstance, to be disadvantageous and hence becomes a disability.

3.5 Comparisons between Disease and Disability

Interestingly, I believe, that there are correlations to be made between the philosophies of disease, and the models of disability. Simple naturalism views disease through the lens of a causal biological malfunction, while the medical model of disability emphasizes that the disability encountered by a person (both social and personal) is a direct consequence from their impairment. Constructivism, as previously described emphasizes that disease should be understood from a values perspective, whereby we value or disvalue certain traits or impairments and subsequently classify them as being synonymous with an impaired state. Naturally, the social model of

disability has many similarities with constructivist philosophy, from the view of extrapolating impairments faced within social environs into classes of disease[10].

Of particular interest are the philosophies of two-tier naturalism and the human variation model. Both concepts consider the well being or suffering of the person experiencing disease or disability, whilst also giving due regard for the causal biological process. Both understand that there are variations of the human form, however it is the presence of suffering or a diminished well-being brought about by an impairment that renders the classification of disease or disability. Stringently differentiating between disease and disability becomes difficult once the two-tier naturalism and the human variation model are elaborated. Two-Tier Naturalism is solely concerned with rendering a classification of disease. On the other hand, the human variation model, depending on the perceived source of suffering, can classify the same impairment as either a disease or disability.

3.6 Suffering

The term suffering is used in two-tier naturalist philosophy, and is inferred in the human variation model of disability, however questions arise as to how it is

[10] An example of a medical and social construct of disability. In a medical construct a person whom is born without legs is unable to walk and it is the fact of being born without legs that labels the person as disabled. In a social construct, having no legs and using a wheelchair is seen as a modality to overcome having no legs, however if a building is not wheelchair accessible, then the social environment has caused the disabling of the person.

defined. Suffering can be both physical, and mental, yet in medicine the term is synonymous with pain. Pain management is routine in many medical disciplines, however one's suffering is often overlooked (Cassell, 2004). There are varying degrees of suffering, which are most often linked to the duration and frequency of a particular stressor. Furthermore, attitudes towards suffering may vary in the sufferer and in other people, and is often inextricably linked to how avoidable / unavoidable, useful / useless, or deserved / undeserved the suffering is (Anderson, 2014). Suffering is common amongst all of humanity in many guises, and yet it is highly individual and subjective. Suffering is paradoxical in a sense, given that we as individuals, or a society can analyse the concept of suffering and refer on past experiences to aid in our understanding of it, yet we are unable to truly understand the suffering experienced by another individual.

3.7 Going Forward

Understanding disease and disability is difficult to do given the vast range of impairments covered by the two terms, moreover the philosophical models and normative constructs utilized to aid in the understanding of disease and disability, are not without their flaws. It is my opinion, that the two-tier naturalist model of human disease, and the constructivist model are the most useful and informative methods to utilize going forward in our discussion on gene editing. Two-tier naturalism provides us with an empirical means to interpret impairments, whereas constructivism provides a

means to interpret impairments through a values system. Furthermore, the concept of suffering must remain ever present when discussing human impairment or enhancement, with particular emphasis on the entity experiencing the suffering.

4. Ethics

Gene editing raises significant ethical questions, which require elaboration on key concepts such as beneficence, maleficence, autonomy, and justice. CRISPR, as a technology, has equipped scientists as well as amateur scientists with the means to carry out gene editing techniques on any subject matter with a viable genome. Thus, while moving forward in this discussion on gene editing, we must be mindful that gene-editing technology will only become more refined and accessible to a wider audience. Gene editing, as previously described in Chapter 2, operates in three key platforms namely; non-clinical, clinical somatic, and clinical germ line. Each platform raises unique ethical concerns regarding the applications, efficacy, accessibility, and safety of gene editing technologies.

4.1 Somatic Gene Editing – Non-Clinical

Currently, the non-clinical applications of CRISPR are more widely applied. Given the sensitivity and specificity, and the low cost of CRISPR technology over former gene editing methods, research laboratories are now able to investigate with greater stability and throughput the gene sequences and pathways central to their research (Harrison, Jenkins et al. 2014).

Navigating the ethics of CRISPR technology in non-clinical somatic cell settings does not come with the obstacles associated with the clinical somatic, and the clinical

germ line platforms. The lack of ethical obstacles, unlike the two other platforms, is because there is no direct human harm. Laboratory experiments in the non-clinical setting are confined to petri dishes and the bench top, and are designed to uncover how genes function in a controlled state and under preselected conditions. Moreover, the majority of the genes studied are from species other than humans, such as mice. Human cells can be used in these experiments once retrieved from either a biobank, or perhaps directly from a patient cohort willing to donate a sample to a research study. These methods of sample retrieval are not without their ethical considerations, however issues such as consenting a patient to donate for non-clinical studies fall out of the remit of this piece.

However, a potential source of harm in the non-clinical setting may be encountered by altering the genetic make up of a species such that it proves harmful to the environment. Such fears were described earlier, when the first attempts of gene editing were associated with the creation of “superbugs” or advanced microbial agents, which could have disastrous effects on the environment, and human health. These harms are still present should genetically modified organisms come into contact with environs other than the sterility of the laboratory. The ethical discourse surrounding this area is plentiful, and as such is not unique to the conversation surrounding the paradigm shift CRISPR has created.

4.2 Somatic Gene Editing – Clinical

Understandably, given the perceived contentiousness of CRISPR mediated germ line editing, somatic cell editing has been less well discussed. According to commentators such as Church (2015) CRISPR is more likely to change the face of medicine through its application of engineering somatic cells to act as the medical treatment, instead of preventative germ line edits. Apprehensions surrounding somatic cell editing are coming to the fore as somatic gene editing technology is already underway in clinical trials and is yielding promising results. Given the similarities of somatic cell gene editing to the practice of organ transplantation, the contextual framework of how we view somatic cell gene editing for medical therapies departs from the framework of germ line editing. Thus two unique questions are raised in relation to the clinical (somatic) applications of gene editing: (i) how should we trial the therapy, and (ii) who has access to gene editing technology.

4.2.1 Trialling Somatic Gene Edited Therapies

Trialling any new medication is not without its ethical concern, but trialling a somatic cell treatment adds another layer of complexity. Recruitment of candidates to a clinical drug trial requires the candidate to be competent to consent, and fully informed and, in the majority of cases, over 18 years old. However, as the aim of a somatic cell treatment is to treat an impairment that has a genetic basis, any interactions on a genetic level could be fatal.

Scenarios where there is a requirement to only consent competent adults to a trial in order to study a gene abnormality have highlighted aspects of maleficence. For example, suppose there are two forms of a single gene disease, called X. There are two presentations the disease can manifest in; (i) a mild form in which the affected person can live a full life expectancy with a good quality of life, and (ii) a severe form in which the person would die in the first year of life. In order to study disease X, adults with the capacity to consent would be signed up to a new drug trial involving the somatic cell gene therapy. However, it is argued, should a participant with the mild variant of disease X die as a result of the somatic gene edited therapy, has more harm been encountered by the competent participant, versus had the trial been performed in an infant with the severe form of the disease? Savulescu (2001) argues that somatic gene editing should be trialled in infants with lethal variants first, and not in adults who already have the mild form of the disease. The idea of this theory is that the risk is minimized to the person who has the better life expectancy.

Evidence in support of the above concern, writes Sibbald (2001) can be found in the case of Jesse Gelsinger. Jesse, an eighteen-year-old teenager was born with a mild form of a metabolic order called Ornithine Transcarbamoylase (OCT). OCT affects 1:40,000 newborns and is associated with the inability to eliminate ammonia from the body, resulting in severe brain damage. Half of newborns do not survive 1 month post birth, while the other half do not survive greater than five years post birth. In Jesse's case, he had a partial gene abnormality, he was able to regulate his condition through

the use of a low protien diet and varying medications. As a result of his partial gene defect, Dr. James Wilson, then director of the Institute for Human Gene Therapy at the University of Pennsylvania, considered Jesse as an ideal candidate to undergo a somatic cell gene therapy to restore the defect OCT gene. In September of 1999, Jesse was given an infusion of a vector system, that was desgined to restore the OCT gene to normal function, through his hepatic artery. Jesse's body mounted an immune reation to the vector construct which resulted in his death four days post injection. While the case is most widely used to discuss the topic of informed consent in medical research for this discussion Jesse's case highlights that we cannot expect to trial a somatic cell gene therapy in candidate whom already has a considerable life expectancy over those who have a significantly reduced number of quantitative life years.[11]

4.2.2 Accessibility of Gene Editing Technology

As previously described, gene editing was once the preserve of high-ranking scientists and research groups who described the gene editing technology of their time as, for want of better expressions, cumbersome and difficult to utilize. Indeed, the initial public apprehension felt by the non-scientifically versed citizens of that time is mirrored by the apprehension felt today. However, the advancements in gene editing technology have been such to allow tangible results in the germ line-editing arena. Moreover, gene-editing technology is no longer the preserve of the aforementioned

[11] Jesse Gelsinger's case is an example of neglecting to inform the participant of the risks and harms involved in the clinical trial. Outcomes of the clinical trials related to animal models, and some of these outcomes resulted in death.

minority, but instead the technology has opened up to the entire scientific community, and, in some settings, the community-at-large.

The sensitivity, specificity, and the associated cost with using CRISPR were the key factors that led to the surge of CRISPR's popularity amongst scientists. Ledford (2015a) details the cost of endonuclease technologies such as ZFN's has an average cost of $5000, by comparison CRISPR platforms can have a total cost of $30 or less. The reduced cost is by no means an indicator of reduced functionality, rather it reflects the simplicity of the platform to design and manufacture. The coupling of low cost, and high sensitivity and specificity has led to questions of CRISPR's applicability and safety in both somatic and germ line treatment modalities. Efficacy of CRISPR is continually improving, and it is forecast that the teething issues regarding off-target mutations will begin to fade. Understandably, there is a significant beneficence claim to be made with the reduction in cost of somatic gene editing technology, as with more research laboratories accessing the technology there is a proportional output of knowledge.

Modern day science has allowed for the introduction of "community laboratories" attended by do-it-yourself amateur biologists called "biohackers." Biohackers, explains Ledford (2015b), usually work within the confines of the lowest level of biosafety precautions needed to implement their techniques, straying outside of those confines in some European countries is illegal. Most biohackers have benign

goals, which generally do not surpass the creation of edited yeast strains to confer different tastes to beer. Scientific opinion is torn with regards the remit afforded to biohackers. One side wants to nurture public enthusiasm in science, and empower people to engage in debate and scientific inquiry through practical experience. Meanwhile, other commentators approach biohackers with much more caution, as it is within this community that much of the maleficent qualities associated with low cost gene editing technologies lie. These commentators argue that providing such powerful techniques to people with no formal training and removing them from a regulated research laboratory, answerable to no regulatory body, opens up the possibilities for misuse of the technology on a much wider scale.

Importantly, it is mutually agreed that biohackers and to some extent scientists will, for the most part, be unable to edit embryos without access to: funding, correct equipment, licenses etc., it is also understood that the more refined and accessible CRISPR technology becomes the more likely people will begin to tamper with human biological material. This biological material will most likely be somatic cells, such as skin, or blood. Ergo, a unique quality of somatic cell gene editing is that, the source material and the technology are readily available and thus are more likely to be experimented with by scientists and biohackers. Moreover, this experimentation is contextually significant dependent on the intentions of the individuals using the gene editing technology.

4.3 Germ Line Gene Editing

By far the more contentious and hotly debated platform for gene editing technology is the human germ line. Germ line gene editing is a multi-faceted ethical topic, however three distinct categories of ethical concern are identifiable: (i) the clinical applications regarding impairments, (ii) sanctioning research, and (ii) clinical applications regarding enhancements.

4.3.1 Clinical Applications

Many commentators have been quick to scrutinize germ line editing in relation to pre-genetic diagnosis, therefore analysing the discourse of germ line editing versus pre-genetic diagnosis (PGD), and applying the community values outlined in chapter 3, a clear distinction can be deduced between the two modalities. Moreover, through applying philosophies of impairment to exemplary case studies, issues of autonomy and justice are conceived.

4.3.1.1 Gene Editing versus Pre-Genetic Diagnosis (PGD)

Using gene editing to avoid an impairment manifesting is morally equivalent to the standard conventional treatment of that impairment. However, this moral equality is not true for selection given the non-identity problem, which incorporates the concepts of person affecting harms, and impersonal harms (Woodward 1986). Person

affecting harms are most often attributed to gene editing when there is a suitable medical modality already in place, meaning that both gene editing and the medical modality would confer an ideally normal and healthy life to the person undergoing treatment. To withhold either the gene editing or the medical modality would cause the persons condition to deteriorate and may end in death, essentially withholding either treatments is harmful to the person. Impersonal harms are more frequently encountered with the use of screening techniques such as PGD. In the case of PGD, if parents decided not to screen their embryos for an impairment, then their child would have a 30-year life expectancy; this is assuming the child deems their life worth living. However if the parents decided to screen their embryos and did not select an embryo with the genetic hallmarks of the mentioned impairment, then that child would never have come into existence, and therefore would not have been harmed (Savulescu 2001)

There are, however, certain cases where PGD may be a better method to use in comparison to germ line editing. In the first case two adult parents select an embryo that displays the genetic characteristics of an impairment. This embryo, once it comes into existence, has no claim that its parents have deliberately caused harm. The only harm that could be encountered by this child is that if it's life were not worth living. In the second case, two adult parents use germ line editing to insert an impairment into an otherwise unimpaired embryo. In this case, the child that comes into existence has a

claim that they have been harmed, as if it were not for the actions of the parents the child's life would have, in their opinion, been worth living.

Furthermore, considering the above cases, PGD may prove more beneficial in scenarios where there are uncertainties surrounding gene interactions. It may be the case that to edit gene A, one must also accept the deletion of gene B. Gene A is attributed to the normal functioning of a biological organ, whereas gene B is attributed to a mental skill. In this circumstance, the environment of the future person must be considered to decide if a normal functioning biological system with a diminished mental skill, or decreased biological function with an intact mental skill is more advantageous. Should the parents opt for either, the resulting child has a claim that they have been harmed. Using the same scenario and applying it to PGD, the parents may elect to use the embryo that naturally has an impaired gene B, and a normal gene A, meaning the resulting child has no claim to say they have been harmed as they inherently never had gene B, their only complaint would be that life was not worth living.

Fundamentally, the key difference between germ line editing and PGD is that germ line editing removes the defect or disvalued gene from the embryo, meaning that the subsequent progeny will not have the genetic impairment and will not be able to pass it on to future generations. PGD is confined to the prospective parents choosing

the embryo most suitable to them and may in some cases entail a trade off regarding genetic make up, however germ line editing is a decision to remove, insert, or edit a germ line gene sequence in order to confer a preferred state of normality. PGD, unlike germ line editing, does not entail the elimination or addition of a gene sequence; rather the gene is not expressed in society, as the embryo exhibiting the disvalued gene had not been selected.

4.3.1.2 Futility of Stringent Differentiation

The term “a life worth living” has been used multiple times throughout this piece, however an exploration into its meaning has yet to occur. In my opinion, a life worth living is not the same as a life without suffering, similar to health, where health is not solely based on the absence of impairment. In order to understand the term “a life worth living” we must apply the philosophical concepts encountered in Chapter 3 to states of impairment as they relate to the society and to the individual.

The term “a life worth living” is a very individual one, and it is difficult for another individual or party to empathize, relate to, and understand the unworthiness of life felt by another individual. In essence, the only person who can decide the worthiness of living their life is the individual living that life. It is difficult to define what characteristics determine whether a life is worth living; it is my opinion, that the WHO

definition provides a better description of a life worth living albeit with some slight modification, than it does for its intended purpose of describing health:

"Health is a state of complete physical, mental and social well-being and not merely the absence of impairment."

Editing the above quotation to the following;

"A life worth living is an acceptable level of physical, mental and social well-being, as experienced by the individual, and is not merely the absence of disease or infirmity."

Suffering, as previously described, is an integral part to our impairment philosophies, yet suffering's contribution to "a life worth living" is not as clear. What one individual may experinece as suffering (physical, mental, or emotional) another individual with the same impairment may not experience the suffering described in the first individual. It is therefore, imperative that an understanding of how the philosophical concepts of impairment are discussed in relation to impairments and applied to case studies.

Simple naturalism and the medical model of disability fail to take into consideration the concept of suffering, however their refreshing simplicity makes them the popular models in daily healthcare provision, rather than academic discourse. Two-

tier naturalsim is a more robust adaptation of simple naturalism, as it allows for the interpretation of suffering. The suffering experienced is predominantly encountered at an individual level, the very fact the person has the biological impairment, coupled with any experienced symptoms is what qualifies impairment in this model.

The social model of disability is often used by disability rights activists as a means to articulate that it is not the impairment of the person that is disabling, instead it is society's unwillingness to accommodate people with these impairments that causes the disablement. The social model of disability works well in some cases such as when a person is involved in a road traffic accident and loses use of their lower limbs. This person is not disabled until a public space fails to accommodate wheelchair access, thus the person is not disabled simply by having non-functioning lower limbs, but is diasbled by not being able to overcome having non-functioning lower limbs with the use of a wheelchair.

The human variation model of impairment is a neater evolution of the disability construct, however remains imperfect. The human variation model understands that there is a biological underpinning to the impairment, but also gives particular regard to the suffering experienced to the individual, both society inflicted suffering and the innate suffering caused by virtue of having the impairment. Therefore under the human variation model Person 1 for example, who is deaf may not suffer as a result of

being deaf, is a human on a spectrum of normality and is therefore not disabled. Person 2, may suffer as a result of being deaf, should the suffering stem from a societal inability to accommodate this impairment then one may assume that being deaf in this situation is a disability. Person 3, may be the same as Person 2, only they are suffering as a result of intrinsically being deaf, one may then understand being deaf as a disease.

Constructivism, does not initially appeal to orthodoxy, particularly in modern medicine. However constructivism philosophy highlights a unique individual and societal trait when tested against impairments. On an individual level a person may feel that they are suffering and that their life is not worth living, conversely, that same individual may then realise that through their suffering something new has developed (e.g. forging a new relationship) which has now made their life worth living. Similarly at a societal level, society may disvalue the suffering endured by an individual with a certain impairment, but simultaneously society may value another trait exhibited by the suffering individual, such as bravery. In essesence, constructivism removes the need for the human variation model of disability as it solely caters for value judgements and does not require an emperical foundation which is already provided for through two-tier naturalism. Constructivism helps us understand the unclear cases faced in medicine, such as life limiting impairments, and the value of advocating for autonomy.

4.3.2 Case Studies

4.3.2.1: The Verbessem Case (Waterfield 2013).

The case of Marc and Eddy Verbessem, two Belgian twins, illustrates how impairments that society deems strictly as disabilities, can make ones life unworthy of living, and interfere with ones autonomy. Marc and Eddy were both born with congenital deafness, communicating to themselves and their immediate family with their own unique form of sign language. At the age of 45 both men developed glucoma related blindness. Belgium's euthanasia laws allow for the euthanaisa of a patient once that patient can make an informed decision, and that the physician judges the patient to be in unbearable pain. While the Verbessem case was not centered around physical pain, nor were the men terminally ill, it hinged on the fact that there was unbearble psychological suffering endured by the twins. Importantly, this psychological suffering was in tandem with their impairments. Analysing this case highlights that the suffering felt by a person with impairments may have nothing to do with society not accomodating these impairments, instead it was caused by the prospect of not being able to see or hear one's twin brother.

Both Eddy and Marc were aged 45 at the time of their assisted suicide, and were persistent in their efforts to access a hospital that would perform the euthanasia. However, their efforts and autonomous choice's were dampened with doubts and

concerns presented by their family and society. Mr. Verbessem, the father of Marc and Eddy, was quoted saying:

"I sometimes think that if they had their own wives and children, perhaps they would have something to live for."

While I agree that some things in life are unexpected and may be life changing, there also exists the very real and serious consequences of continuing on with ones impairments should they have already deemed them as making their life unworthy of living[12]. Furthermore, there were educated voices in society raising their concerns over the assisted suicide of Marc and Eddy, most notably from Prof. Chris Gastman, a medical ethicist at the Catholic University of Leuven (Waterfield 2013). Gastman addressed a fear of the wider implications of the Verbessam case on the welfare of disabled people;

"In a society as wealthy as ours, we must find another, caring way to deal with human frailty."

[12] One must also consider the logistics of whether either of the Verbessem twins could adequately care for their children, should they have had them.

Interestingly, Gastman seems to redefine the meaning of disability when addressing the Verbessem case, as not only does he see their impairments as signs of frailty, rather than disabilty, he also goes as far as to disable them from making their own autonomous choice in wanting to undergo physician-assisted suicide.

The Verbessam case shows us that our understanding of impairments changes depending on the philosophical models used. Some in society viewed the Verbessem twins as disabled through constructivism, however the twins themselves viewed their impairments through a two-tier naturalist perspective which classified them as having a disease which merited treatment[13]. Furthermore, the twins had no choice in the suffering they had to endure, neither had their parents, as the impairments were genetically rooted, meaning that the genetic abnormality was indiscriminate of whether the resulting impairment was societally classified as a disease or disability. Thus, classifying impairments as either a disease or disability can cause tension between stakeholders regarding any genetically based impairment, and result in the diminishing of autonomy for the person with the impairment.

[13] The treatment sought by the Verbessem twins was euthanasia.

4.3.2.2: The Bannon Case (Pelletiere 2016)

Linda Bannon, was born with Holt-Oram Syndrome, a condition characterized by abnormal upper limb skeletal development, and some heart conditions. In Linda's case she was born without arms, however according to her:

"It never really occurred to me that I was that different from anyone else."

After Linda met her husband, and she conceived a child, Linda was made aware by her physician that the option was open to her to terminate her pregnancy should her condition also be present in the developing embryo. Linda refused the option to terminate the pregnancy, as it was her main wish in life to have a family and children. Her son Timmy Bannon, was born with Holt-Oran Syndrome, and spent his first months of life in intensive care post cardiac surgery. Several years on however, both Linda and Timmy refuse to wear prosthetic limbs, and both lead a particulary active and engaging life style. According to Timmy:

"I'm just like all the other kids."

In the Bannon case, we can see that the mother's choice not to avail of a termination of pregnancy, brought a child with an impairment into the world, which is

in stark contrast to the aforementioned Verbessem case. However, judging from the case, the childs life is, in his opinion, worth living. Here is a case where the impairment described, while associated with a biological abnormality, has not resulted in suffering therefore allowing both mother and son to lead, in their eyes, a normal, unimpaired life. Interestingly, when we view the Bannon case through the lens of germ line editing there is a shift in logic and perhaps potential consequence. Anecdotally, assume the mother was faced with two scenarios: (i) edit out the gene for Holt-Oram Syndrome from her embryos resulting in a child that had no upper limb skeletal abnormalities, or (ii) insert the gene conducive for Holt-Oram syndrome into an embryo that was void of that gene.

In scenario one, the mother made an informed decision to edit out the gene that would cause an impairment to her child. Naturally, in her view this may have stemmed from a place of beneficence, meaning her child could live his or her life without the need to adapt or overcome Holt-Oram Syndrome. This option is maleficent perhaps when viewed from society's perspective where hypothetically there may be more than adequate resources to facilitate her child with Holt-Oram Syndrome. In scenario two, the mother may have wanted to have a child that she could relate to, and in turn her child could look up to as a role model for the impairment. This may be the situation in one case, however the child may feel that they have been harmed. The harm described by the child in scenario two may be that their life has been unnecessarily burdened by the impairment, and in some cases they may also claim that

their life is not worth living. Claiming their life is not worth living, even though there may be infrastructure in place for them to overcome their impairement, is valid when their suffering is considered. Much like the Verbessem case, where sign language and brail are modalites for deaf and blind people, respectively, to overcome their impairments, societies infrastructure or, lack of, may not be the place where ones suffering lies. Instead, the suffering encountered here is individual, and unopen to societal opinion and critique.

Overall there is a key distinction between the Bannon, and Verbessem cases which is rooted in autonomy. The Verbessem twins actively sought to end their life as a mode of treatment for their impairments, whereas in the Bannon case, the mother actively sought to have a child with impairment, unknowing of the degree of suffering that her choice may have entailed. The autonomous choices of allowing an impairment to come to fruition versus the choice to treat an impairment, seems to strike a societal chord, in which the reaction to someone treating an impairment that is societally deemed as a disability is to reduce the impaired persons autonomy. Oppositely, a societal appetite for the patient to undergo treatment strengthens the autonomous choice in cases of disease. Commentators often allude to how as a society we often judge disabilities as much worse than they often are, however little regard is given to those who have a disability and regard it as a disease.

4.3.2.3: The Dunford Case (Dunford 2016)

Kevin Dunford was born in 2005 with an unspecified life limiting condition, writes his mother for the Journal.ie (2016). Kevin's condition meant he lived a life of medicalization, however as his mother describes, as Kevin's physical being became weaker his appetite for life became stronger. Kevin's mother describes all the facets and hallmarks exhibited in any young child's life, however there was an ever present sense amongst his parent's at least, of how his condition would culminate. As of 2014 Kevin began his stay at the LauraLynn hospice for children. Through the experience of their son undergoing palliative care, Kevin's parents reflected on everything their son taught them in his short life:

"He taught us about dignity, fun, patience, gentleness, joy and friendship"

While the article was written from the perspective of praising the quality of palliative care Kevin received, I believe Kevin's case, as well as many others like his, serves as a perfect example for our discussion on impairment and germ line editing.

Kevin's impairment was life limiting, however from his parent's perspective there was immense value in his life. We cannot assess Kevin's perspective on whether he believed his life was worth living. The suffering, in Kevin's case, is difficult to infer, while no explicit reference is made in relation to suffering, there are some quotes that lead me to believe that suffering certainly did have a part to play in this case:

"Physically, Kevin was entrapped in a body that grew weary as the years passed"

"LauraLynn came in our family's life at a time when Kevin was weaker physically"

"A room we dared not think about in life; but cherished in death."

Kevin's story is harrowing, and one of particular interest from a germ line editing and bioethical perspective. Kevin's case illustrates a scenario whereby a child faces a life threatening disease, however even in the face of a fatal impairment, aspects of the impairment are still valued for what it imparts by way of experiences, life lessons, and memories. This scenario now raises the question of, if germ line editing was available to treat the impairment encountered by Kevin, and many others like him, should it be utilized?

Referring back to Kevin's mother's description of what cherished and valuable lessons he taught them, one may argue that perhaps these were only taught as a result of Kevin's impairment. Understanding this point of view is better understood when analysed through the philosophical concepts and models of impairment.

4.3.2.4 Application of Philosophical Concepts of Impairment

Firstly, the medical model of disability and simple naturalism do not lend themselves to understanding why a person with a life limiting impairment has a life worth living, as they only appreciate the biological malfunction. Two-tier naturalism, acknowledges that there was some suffering experienced by Kevin and his family, and acknowledges that there is an underlying biological abnormality. Two-tier naturalism, in this case only tells us that the impairment in this scenario is a disease, it does not inform us as to why it may be valued. The social model of disability, in my opinion, does not fit with the described scenario, as the model is only concerned with how a person with a disability is disabled by society and how that disability causes suffering. The human variation model, however, while slightly better for the understanding of this scenario, still falls short. This model acknowledges that there is a biological underpinning to the impairment, but surely significantly diminishing the number of life years of a person is beyond the remit of normal human variation, surely variation of this magnitude begins to fall into the fringes of the human variation spectrum. Furthermore, this model acknowledges that there is suffering present, but faces the same stumbling point as encountered with two-tier naturalism.

Constructivism, in my opinion, is the best method to understand how a life limiting impairment may be valued or disvalued. Constructivism understands that there is suffering present with the impairment both personal and shared, but the life of the

person with the impairment is worth living and valued. Constructivism allows the user to apply a values perspective to an impairment, that the other philosophies and models do not allow us to perform. The life of a person with a life limiting impairment is in some cases worth living because of the life lessons, and memories all stakeholders get to experience. In these scenarios, suffering may be experienced but it is overcome by qualities that we value such as resilience and bravery. Constructivism lacks the qualities of two-tier naturalism, but makes up for it by enabling the user to apply a values approach to impairment. Thus, one can be both a two-tier naturalist and a constructivist when analysing impairments. Kevin's case alongside constructivist philosophy highlights the role, albeit a difficult truth, that impairments have in human life.

These cases highlight that it is futile to consider impairments as either diseases or disabilities, if the autonomy of the person with the impairment is going to be compromised in the process. Currently, as a society we might encourage germ line editing measures to remove the prospect of cancer or neurodegenerative disorders from a person's life, however in the cases of perceived disabilities questions arise over how to find common ground. Common ground is difficult to find particularly when one stakeholder believes an impairment to be a disability, and another believes it to be a disease, furthermore one must also take into account that one of these stakeholders may be the impaired individual. Added complexity is encountered when one views impairments and associated suffering as still being compatible with a life worth living.

Regimes of germ line editing when there is no definite societal desire, inclusive of all stakeholders, is therefore futile to implement.

To conclude, the totality of germ line editing over that of any other conventional medical therapy, is what fastens its controversial application as a medical modality. The totality being referred to is the sequential elimination of unvalued genes from the species. Once germ line editing begins for a class of diseases, over time those disease-causing genes become diluted out of the human gene pool and are on a trajectory to extinction. Furthermore, once the incidence of the disease, which has been edited out of the germ line, begins to significantly decrease, the apprehension of some commentators that society will then turn to another disease to edit out becomes all the more real. Questions begin to come to the fore regarding the point at which we begin to reach a plateau where all significant diseases are in the process of being edited out of the germ line, do we then medicalize superficial traits that we disvalue? In essence, while not slipping into the “slippery slope” argument, which will be discussed later in this chapter, will the species once germ line editing is introduced continually find or label a trait as an impairment in order to bring about its editing?

4.3.3 Autonomy

Autonomy is defined as the right to one's self-government free from external control or influence. Autonomy, is much more complex when applied to the field of germ line editing, however in relation to somatic cell therapies, autonomy can be viewed in the same respect as any other medicinal therapy. Somatic cell therapies function similar to organ transplantations, however cells are harvested instead of full organs, and then transplanted back into a patient. The editing of the somatic genetic material is less controversial than germ line editing as the changes are strictly confined to the person undergoing the therapy and are therefore not heritable. Furthermore, the patient in somatic cell therapies must satisfy tests of capacity and consent before administration of the somatic cell therapy. In essence, somatic cell therapies, although there is a molecular intervention, ethically function no different to red blood cell transfusions.

Autonomy when applied to germ line editing uncovers many ethical quagmires. One of the most obvious hindrances to autonomy is the ability or the option to use germ line editing in the first place, as it may impose a sense of responsibility to use germ line editing not just for oneself but also to use it in the interest of society. Anecdotal evidence of being able to make a choice at the very early stages of embryonic development can be inferred from data relating to terminations of pregnancy post Down-Syndrome diagnosis (Hayden 2016). The incidence of Downs-

Syndrome in 1990 was 20/10,000, and as of today the incidence is at 23/10,000, this increase as been attributed to the increasing average number of women having children. However the number of births with Down-Syndrome children has remained consistent at an incidence of 11/10,000, this consistency has been attributed the termination of pregnancy once a diagnosis of Down syndrome was provided. It is estimated that between 67-85% of pregnancies are terminated in the United States once a diagnosis of Down syndrome is discovered. Furthermore, according to a study compiled by Skotko, Kishnani et al. (2009) physicians had a significant role in whether a woman decided to undergo a termination of pregnancy, because of the physician's contextual language. Examples of this influential language of when a diagnosis of Down syndrome was discovered are:

"I have some bad news to share" and

"I'm sorry."

Moreover, the study highlighted that 34% of 71 Dutch women who underwent a termination of pregnancy said that their physician did not even consider the option of continuing the pregnancy when discussing their options.

Germ line editing of the genome to remove, for example, Down-Syndrome from the developing embryo raises another ethical concern unseen with the termination of a pregnancy, that being the removal of Down-Syndrome from future generations. As can

be seen from the above statistics, there are still children being born today that have Down-Syndrome, and there are still humans present in the world that are carriers for Down-Syndrome, meaning that Down-Syndrome will always be present in the human genome. This presence however may be removed through the continual use of germ line editing. Over time, if germ line editing were implemented in one generation, successive generations would be exponentially diluted of the Down-Syndrome genetic profile until its extinction. As a result, these edits significantly change our attitudes about what kinds of people matter in the world today.

A unique concept uncovered by the doctrine of autonomy is that there is both an individual autonomy and a species autonomy regarding the human genome. Obviously, the rights of an individual encompass their genetic autonomy, however I believe that as a species we have a collective vested stake in the human genome. Naturally, I do not believe that an individual can infringe on another individual's genetic autonomy directly on the basis that they are acting in name of the species. However, I do believe that as a society we must have a debate, if we decide to implement germ line editing, on what genes are permissible to edit in ones genome for the betterment of the individual and society.

Developing from the concept of a collective species autonomy we now move from a discussion on the genes that we disvalue in society, which may be attributed to

specific impairments such as certain types of cancer, or neurodegenerative disorders, some disabilities such as deafness or blindness, to a discussion on how to enhance the human genome. Naturally, the removal of genes associated with the impairments mentioned above can be seen as an enhancement to the human species as well as a medical modality.

4.3.4 Justice

Often overshadowed in the debate by topics such as clinical efficiency, and ethical quagmires, justice is a major factor if germ line editing procedures are to be introduced. Germ line editing will prove to be extremely costly to implement, given the degree of research and development undertaken to bring this technique to a routine healthcare setting. Thus, issues arise surrounding the ability of people to pay for germ line editing technology. If germ line editing is the preserve of the wealthy, then those marginalized in society only become more disenfranchised once the wealthy in society are able to have wealth as well as health. However, from a State perspective, it does not seem to make much sense to introduce germ line editing to the healthcare matrix, and not fund it in some manner as to allow lower socio-economic classes to avail of the technique. After all, germ line editing is preventative rather than therapeutic, meaning a substantial saving on therapeutic modalities could be made if germ line editing measures were supported and funded by the government of the day.

Government initiatives, however, no matter the degree of opportunity or coercion, still see the lower socio-economic classes fairing worse than their wealthier counterparts (Walsh 2016). Evidence released by the National Cancer Registry of Ireland highlights the cancer inequalities faced by people in lower socio-economic classes with up to a 40% disparity in mortality between the higher and lower socio-economic classes for certain types of cancers. Questions subsequently arise surrounding the implementation of germ line editing and whether it is a stand-alone treatment or whether investments need to be made in the environmental circumstances of the edited progeny. Voluntary germ line editing as a preventative measure for disease may be the most plausible way to introduce germ line editing into a healthcare system, however state enforced coercion may see genetic predispositions or impairments fall into the scope of the editing regime. However, preventative medicine in the Western world is still in its infancy where screening and vaccination are the two main techniques used, it would therefore be a rather large jump to implement nationwide germ line editing as a tool for preventative medicine. The more likely scenario therefore is initially the technology will most likely only be available to those that can afford the treatment.

A popular area of ethical commentary is editing genes to remove a predisposition to a certain behavioural trait, such as violence. Brunner, Nelen et al. (1993) found that violent tendencies in men of a Dutch family were linked to a shared point mutation in a neurochemical, monoamine Oxidase A. This point mutation led to a

decrease in a chemical called 5-hydroxyindole-3 acetic acid in the cerebrospinal fluid, which was associated with impulsive acts of aggression. While this study was confined to one family there is significant debate surrounding the role of genetics in criminal and violent behaviours that are disconnected from environmental conditions.

Attention Deficit Hypersensitivity Disorder (ADHD), write Morley and Hall (2003), is a behavioural condition characterized by an inability to remain focused and keep attention on one particular thing or activity. ADHD when displayed in children has a high chance of being carried into adult life where an impulse control dysfunction and the presence of hyperactivity are factors highly correlated to the presentation of anti-social behaviour. People with ADHD, are also at a higher risk of developing Conduct Disorder (CD), which is a condition characterized by an individuals violation of societal norms (Morley and Hall 2003). Coupling ADHD and CD together, present the risk of the person further developing Antisocial Personality Disorder (APD), which is diagnosed in people over the age of 18 years old, and who have a persistent disregard for the rights of others, coupled with an increased propensity for criminal activity. In essence society is faced with the situation whereby the criminal in this context, is not primarily a victim of circumstance and environment, rather a victim of an inherent biological impairment with manifestations of actions that society disvalues.

Examining violence and criminality through the lens of gene editing reflects the collective values of a society and forces it to examine whether it disvalues the person with the genetic impairment or disvalues the genetic impairment that has manifested itself in the actions of the affected person. Moreover, we are forced to decide as a society if we value the life of the affected person to the extent of helping them through their impairment or do we believe that editing the impairment out of the genome completely is the better way forward. These questions are, inherently, difficult to answer as society is acting on the assumption that it knows what is best for the person with the impairment. One could reference, Burgess's 1962 novel *A Clockwork Orange,* where the protagonist undergoes psychological conditioning to remove all violent propensities from his person, however removing his violent qualities turns him into a depressed, emotionally hollow man that seeks to end his life through suicide. While the novel does not use a gene editing method to remove violence from the character, it does illustrate that violence was a fundamental part of character and its removal drastically changed him mentally and emotionally. Treating violence highlights a dichotomy between helping an impaired person through the impairment with adequate infrastructure and socio-economic changes, versus the collective societal and state appetite for convenience that gene editing offers.

In essence, violence could be replaced by any other trait or characteristic disvalued by society. Examples being a genetic predisposition to obesity, which may, throughout the affected persons life, have a disvalued burden on the State's healthcare

system. Society, through State regulation, could change the environmental factors that lead a person to live a life of obesity, or it could advocate for future embryos to undergo gene editing to remove genes associated with obesity[14].

Justice in the world of gene editing seeks to benefit the collective will of society through State regulation or coercion, yet the maleficence associated with gene editing is the burden of the disenfranchised minorities who endure unedited or forced edited lives at the behest of a collective societal will.

4.3.5 Sanctioning the Research

The discussion of germ line editing and the clinical applications offered by the technology often overshadow some pertinent points of debate in the germ line-editing story. Before clinical applications are realized significant amounts of monetary investment, and scientific research from all over the world will have occurred. Therefore, before a discussion on the clinical applications even begins, the primary question we should be asking is should we as a society even allow the research to take place?

[14] Whether State regulations are strictly enforced or voluntary still does not remove the issue of coercion. A state may enact legislation that makes it increasingly difficult for obese people to function as part of society. These constraints may coerce them into "doing the right thing" when having a child, which would be to gene edit their embryo.

Unlike somatic cell gene editing where the sources of cells are readily available, germ line editing will need to use embryos as the subject of the research. The moral, ethical, and legal discourse concerning the use of embryos in research is all too plentiful, however for the purposes of this piece an elaboration will be given on the status of the embryo as it relates to the field of germ line editing. Developing from the status of the embryo in germ line editing, the second topic faced by sanctioning germ line research is the "slippery slope" argument wherein the message is that once the process of germ line editing starts there will be no turning back, and the results of the procedure will only be disastrous. This argument is generally ill supported with factual data.

4.3.6 The Status of the Embryo in Germ Line Editing

Safety is of paramount concern when developing any new medical treatment, however CRISPR's stumbling block in relation to germ line modalities is that it requires embryos to carry out the research on, before it can be implemented as a fully pledged treatment. Questions now arise regarding what entity should be kept safe when using CRISPR for germ line research given the current degree of off target mutations encountered. In essence, are the current safety risks posed by CRISPR germ line editing strong enough to merit an out right ban of germ line editing. The conception of any new medical treatment has always been scrutinized until deemed safe in its preliminary

stages of application. When discussing CRISPR germ line editing two potential stakeholders are evident: (i) the embryo, and (ii) future generations.

In our discussion of germ line editing an ever-present question is "can an embryo be harmed?" Mill (1859) describes harm as being permissible when it is to reduce the harm of others:

"The only purpose for which power can be rightfully exercised over any member of a civilized community against his will, is to prevent harm to others."

The potential for embryonic research is vast, however there remains a significantly loud opposition within society that believe it is wrong to utilize an embryo for any form of medical research. The most common argument put forward by this opposition is that embryos are persons (the moral status of the embryo). Given the embryos moral status amongst this cohort of people, the embryo is attributed equal rights and claims as a fully developed human adult. To many in society and in the medical community this view is implausible, and from dissecting the views implausibility, we can better understand why the safety concerns surrounding germ line editing can be quelled.

First, writes Douglas and Savulescu (2009), there is a disconnect between our intuitions of what qualifies as a human person versus what we, in a given situation,

deem to be a person. Stretton (2008) described a thought experiment detailing a burning IVF clinic and a passer-by's opportunity to save one adult human life versus 200,000 frozen embryos, forces us to critically analyse our intuitions of personhood. Furthermore as described in Leridon (1997) 50%, or 220 million embryos are spontaneously aborted worldwide within 8 weeks of development. Interestingly, the deaths of these embryos are not afforded the same societal rights of passage, e.g. giving a name, and a burial, as their supposed fellow adult human counterparts. Furthermore, it is argued that if there are 220 million deaths of human persons occurring each year, then surely our medical priorities should be focused on saving these persons. This assumption would therefore require the redirecting of funding from research such as cancer, AIDS etc., and rechanneled into research to prevent spontaneous abortion. I believe, that to any reasonable reader this shift of medical priority seems implausible. Therefore, we are left with two possible situations: (i) embryo's are not recognized as persons however we do attribute a graduated level of moral status, and (ii) embryo's are persons but with a special class of moral status, meaning they do not have a right to be rescued from natural or accidental death.

Interestingly, argues Douglas and Savulescu (2009):

"When embryo's are not part of a plan to extend or form a family, they can still have a special moral value: as a means of extending knowledge and saving or improving the lives of people."

Savulescu (2002) states that even if an embryo could be minimally harmed, does it still merit a prohibition of using germ line editing technology. Moreover, in relation to harming an embryo, Savelescu references destructive forms of contraception routinely used by people such as intra-uterine contraceptive devices, the oral contraceptive pill, and abortion, and questions why these modalities are largely accepted in comparison to germ line editing.

Moving on from the harming of embryos', a more plausible harm of germ line editing is that encountered by future generations. The germ line edited progeny will be the sufferers of the potential off target mutations, however a neat solution to this, writes Savelescu, is to ensure that the progeny are not born. If no children are born because of the research the children are not harmed. This concept is neatly shown in Liang, Xu et al. (2015) paper, in which unviable human embryo's were used, meaning that no harm would ever be experienced by an entity undergoing the research.

One may consider the option of editing the male and female gametes, the sperm and ovum respectively, before their fusion to create an embryo that has not received gene editing directly. Instead of editing the embryo, which to some may be deemed as a person, editing the sperm and ovum may not tamper the sanctity of the resulting embryo. Indeed, paternal smoking has been attributed to adverse outcomes in pregnancy including loss of pregnancy, as the cigarette smoke has had mutagenic

effects on the sperm. Surely, manipulating sperm using CRISPR should prove no less objectionable to those who oppose editing the embryo. Alas, there is significant evidence to show that molecular work in haploid cells is particularly difficult to implement, not to mention the difficulties researchers would also have to be overcome to fuse to edited haploid cells to form a viable embryo. As such, editing the embryo is still the only viable means to introduce a germ line edit.

4.3.7 Developing the "Slippery Slope" Argument

The slippery slope argument is one often put forward to try to halt the realization of germ line editing techniques, on the assumption that we do not know, or cannot foresee what our endeavours might lead to, with the result usually being catastrophic. The slippery slope argument does not satisfy reasonable ethical debate and inquiry, yet there is something to be said for understanding the consequences of one's actions and how they may affect another individual or individuals. Therefore, in an ethical discourse, the slippery slope argument can be reworked into an investigation of what we know to be: (i) outright unintended consequences, (ii) a contextual shift of what was once an intended consequence.

It is well documented that many diseases and disabilities do not lend themselves to one key genetic abnormality, rather there is an accumulation of genetic factors (such as inherent predisposition, and exogenous environmental factors) that

can be attributed to the development, relieving, or worsening of a genetic malfunction. Consequentially, editing the genome via the germ line can have negative consequences for future generations, which may have been unintended but may have also been intended changes that soon turn out to be disadvantageous. Unintended harms come by way of off target mutations experienced by the patient who underwent gene editing, and our misguided intended consequences come by way of editing a gene that is disadvantageous in a current generation, but becomes advantageous in another generation. Furthermore, the gene that is disadvantageous in one generation may also have had links to another set of genes, which when deleted, diminishes the functioning of the other genes, thus compromising the stability of the patient's genome.

Maleficence, it is argued, will occur due to a "ripple effect" once gene editing is sanctioned. It is argued that just a few changes to the genome in one generation could have an exponential effect in the subsequent generation. However, in rebuttal to these claims, proponents of gene editing state that it is unlikely that a small number of edited genes would have such global effects, given that there are many other factors undertaken by humans that have mutagenic effects on the stability of the germ line, such as smoking and drinking during pregnancy, and delaying paternity. It is argued that the above factors pose an equal, if not greater risk, to the germ line and therefore it is perplexing why gene editing is prohibited, while the others are unadvisable. Moreover, by this logic once the harms encountered by germ line editing are decreased

by way of efficiency the technology should be less harmful than the aforementioned human factors.

Maleficence, in terms of our intended actions, is experienced through editing a gene that is disadvantageous or advantageous in one generation, but which may be vital or lethal in the lives of the next generation. In terms of a disadvantageous gene, the DARC gene, is known for it ability to “sickle” a red blood cell, and results in a disease termed “sickle cell anaemia” (Oliveira, Harris et al. 2012). While sickle cell anaemia is disadvantageous in western countries, it is partly advantageous in Nigeria, as it confers immunity from infection by the malaria parasite. Editing the DARC gene in the Nigerian population would perhaps, relieve the symptoms encountered with being anaemic, however it would also affect the populations ability to survive an outbreak of malaria, that otherwise they would have withstood. Referring back to Chapter 2, the CCR5 gene, expressed by macrophages, a type of white blood cell, has been linked to the pathogenic effects of HIV. Removing the CCR5 gene from one generation could see a drastic decrease in the number of new HIV cases presenting. However, the removal of the CCR5 gene would cause an increased susceptibility to infections by fungi and parasites, which again could have profound consequences for the following generation.

4.3.8 Enhancement

Enhancement of the human species is prevelant in may forms in todays modern world, one need look no further than the global impact of the health, beauty and cosmetic industry on men's and women's attitude to physical and asthetic enhancment. The sporting industry is also coming under pressure with athletes using performance enhancing methods, some illegeal (EPO), and some legal (caffeine). At an everday personal level, one can see the effects of recreational activities such as alcohol or chocolate intake to alter ones mood. Therefore, our understanding of enhancement seems to be a matter of quality of life, be it for the pursuit of beauty, fame, or relaxation, and less about designing a breed of human that can live unaffected by impairments for a hundred or so years.

Enhancement of the human species through germ line editing can overshadow the debate surrounding germ line editing for therapeutic purposes, as the prospect of enhancing the human species conjures connontations with Nazi era eugenics. Furthermore, genetic enhancement as opposed to germ line editing tends to deal with "softer" gene influenced traits, which generally corrospond to behaviour. Gene enhancements to alter the physical design of a human are also considered, however unlike germ line editing for therapeutic purposes whereby the aim of the therapy is to repair the persons biological malfunction to a state of basal normality, enhancements seek to exploit a genetic trait of an organism to enhance its ability to function in a

specific environment. For example, germ line editing for Duchenne Muscular Dystrophy would repair the defective muscle gene and would result in a child who had normal muscle function, however gene enhancement would see a scenario whereby a child with normal muscle function was enhanced so that muscle mass was increased, therby increasing suitability for physically demanding work.

Genetic enhancement, as outlined in the President's Council Report "Beyond Therapy" (2003) describes, rather damningly, the ill effects of genome enhancement with the view of evolving the human species. This report quotes Sandel (2004) on the detriment that would be caused to the parent and child should genetic enhancement take place:

"The problem lies in the hubris of the designing parents, in their drive to master the mystery of birth. Even if this disposition does not make parents tyrants to their children, it disfigures the relation of parent and child, and deprives the parent of the humility and enlarged human sympathies that an "openness to the unbidden" can cultivate."

Agar (1998) provides an interesting view on genetic enhancement, he believes that enhancement should be permissible but by no means obligatory. Allowing genetic enhancement on a voluntary basis allows for the autonomous choice of a parent to decide their childs ideal genome, thus in theory removing the potential for a society or

State to enforce an “ideal genome.” Once again, Savulescu (2009), appears as one of the main commentators regarding genetic enhancement, and his position is rather pervasive, as he believes that it is societies moral obligation to ensure that genetic enhancement is brought to fruition.

Refusing to enhance the species, Savelescu, argues is a morally neglectful. In essence, if the opportunities and techniques are available to parents to enhance their child’s genome in order for them to realise their full potential, then these efforts should be taken. Savelescu, uses a pill analogy to illustrate how a neglectful and a lazy set of parents failing to provide a pill to a child could see them failing to realise their full IQ potential, thus curtailing their future prospects. Of particular interest are the multiple scenarios in everyday life where a family can substitute the “pill” mentioned above, to any other form of intervention. Should parents fail to provide their children with a healthy diet, they may in turn hinder their child’s prospects in later life, so why is it that we view gene editing in a different light when our intentions are to better the future prospects of children?

Gene editing can in some respects be regarded as a form of treatment when applied to behavioural traits, such as violence. Savulescu, argues that surely the biological route to improvement is no different to the environmental one. Hypothetically, in the case of violent behavourial patterns amongst lower socio-

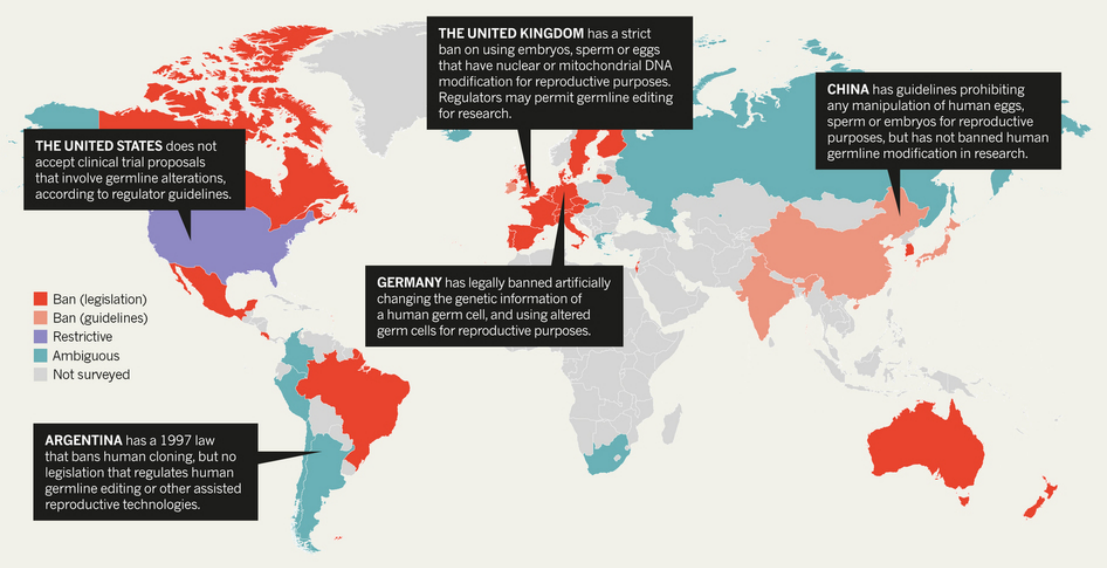
economic classes, enhancing embryos to not display aggressive or violent traits is, according to Savulescu, no different to changing the chid's environment so that the genetic predispositions of violence are not triggered.

Naturally, gene editing with the intention of improving the species conjures connentations with state enforced eugenics. Gene editing, however, can only come into force when there is a public appetite to remove an impairment, or to enhance the species, meaning there may be too much variation in the public voice to come to any meaningful gene editing policy. State enforced eugenics, is only applicable when the State enforces its own vision on a people irrespective of societal appetite. However, there are ways in which the State may be able to introduce gene editing procedures for certain impairments, by way of decreasing funding for an impairment in an effort to coerce people to opt for gene editing to avoid the hardship, and lack of investment by the state in that impairment.

5. Law

Law and regulation is particularly difficult to implement with regards science and healthcare, most often because the advancements being made are outpacing regulation. Therefore, many jurisdictions are left in a situation whereby new techniques and technologies are being critiqued within a legal framework of out dated legislation. Generally, the legislature is reactionary, rather than proactive when legislating for new scientific technologies, moreover the national legislature must also take into consideration any international regulations and treaties that it is a member of, or a signatory to. Analysing law in relation to germ line gene editing (Fig. 3), is problematic, primarily because there are few explicit gene editing laws to reference throughout Europe, and indeed the wider international community. Instead, there are governing bodies, regulatory authorities, acts, amendments, conventions, treaties, and guidelines, which are currently acting as a matrix for our discussion on human gene editing, somatic and germline. There is very little legal uncertainty regarding gene editing and its applications in the somatic cell platform, as other somatic gene editing techniques have been in use prior to CRISPR. Throughout this chapter, particular attention will be afforded to the law regarding germ line gene editing in the following categories; (i) international and European declarations and conventions, (ii) national legislation, (iii) scientific and regulatory body governance, and (iv) proposed models of regulation.

Figure 3: The global legal status of human germline editing Maxmen (2015)



5.1 Declarations and Conventions

On an international and European level there are several declarations that reference gene editing and in some cases reference gene editing and the germ line. Moreover, these declarations are precautionary to preventative in tone regarding the applications of gene editing on the human germ line. Of note, these declarations and conventions predate the publishing of Liang's (2015) proof of concept paper, however many others are in direct response to the study. The United Nations Education, Scientific and Cultural Organization's (UNESCO) Declaration of the Human Genome and Human Rights specifically references in Section G, Art. 24 that:

"Germ line editing" in some cases may be "contrary to human dignity."

Furthermore, the article explicitly references in Section C, Art. 12(b) that:

" Freedom of research, which is necessary for the progress of knowledge, is part of freedom of thought. The applications of research, including applications in biology, genetics and medicine, concerning the human genome, shall seek to offer relief from suffering and improve the health of individuals and humankind as a whole."

Given the discussion in the preceeding chapter regarding suffering, and how suffering can be interpreted based on a individual's, or societal normative ideal or concept of "a life worth living", gene editing research, somatic and germline, for therapeutics and enhancement could theoretically begin with immediate effect, under this declaration. Indeed, this UNESCO Declaration serves, in my opinion, as a particular strong foundation for any government seeking to create legislation concerning gene editing. The declaration covers issues concerning human dignity (Art. 1), the importance of providing a clear and flexible framework for public and private sector gene editing research (Art. 4), and, in my opinion, most importantly stresses under Art. 17, the importance of solidarity and international co-operation. The Declaration, mentions under Art.16 the need for the creation of a "multidisciplinary", and "pluralist" body with the capacity to assess the ethics, law, and social issues raised by human genome editing, this is a point that will be further elaborated on later in this section. It it is important to note at this point that it is widely considered that the UNESCO Declaration

is firmly against germ line gene editing, however, as mentioned, I believe the wording attributed to articles banning germ line gene editing, are slightly counter-intuitive.

Similar to UNESCO's Declaration, the Council of Europe's Convention on Human Rights and Biomedicine speaks about science and its applications to the human more broadly and has a precautionary tone. Under the Council's Convention the research would be permissive in a somatic cell context, however its applications to the human germ line is prohibitive given the clause regarding modifying human descendants. The Council's Convention, also bans human germ line editing, and is perhaps more blatent in Art.13 in its stance in comparison the UNESCO Declaration:

"an intervention seeking to modify the human genome may only be undertaken for preventative, diagnostic, or therapeutic purposes and only if its aim is not to introduce any modification in the genome of any descendants."

Another European regulatory directive, that is not directly related to the field of human gene editing, but has implications in the trialling of any gene editing therapy, is the European Clinical Regulation Reg(EU) No 536/2014. Although the phrasing of Art.90 of the Regulation is, in my opinion, rather odd[15] it nonetheless provides another piece

[15] Ascribing the word "identity" to the genome is, in my opinion, confusing, particularly when we can edit the genome and thus ones identity. Perhaps "profile" would have been more appropriate for this piece of legislation.

of regulation that is permissive in the somatic platform, and prohibitive in the germ line platform:

"No gene therapy trials may be carried out which result in modifications to the subject's germ line genetic identity."

The international and European declarations are, for the most part, definitive regarding their stance on banning human germ line gene editing, however some countries such as the UK, and China are pushing ahead with the use of gene editing technologies and applying them to the human germ line. It may be necessary for the international community to, at least, develop a broad framework or code of conduct which can be easily adopted and interpreted, such that countries can continue to ban, or allow germ line gene editing through their national legislature.

5.2 National Legislation

Equipped with the framework of international and European regulation, national laws, and professional regulatory bodies must then interpret these regulations within the context of their on laws and regulations. Regarding germ line editing, more than 40 countries worldwide have, in some form, laws prohibiting inheritable genetic modifications within humans. The interplay between governmental legislature, and the

role of regulatory or institutional bodies in science and medicine displays a unique dichotomy. Problems can arise, however, when the remit of one party begins to encroach on the laws and regulations of the other party. Generally, the functioning of the professional regulatory or institutional body is provided with the scope by the government of the day, to oversee and implement measures concerning the work and conduct of its members. The problems, mentioned above, arise when the governmental legislation is not in place to back-up the advancements that the professional regulatory or institutional body are making.

For example, in the United States there is no law pertaining to germ line editing, however the Recombinant DNA Advisory Committee, part of the National Institutes of Health, will not accept applications seeking to implement clinical trials using gene-editing technologies on the germ line. Anecdotally in the Irish context, as per Art.13 (2b) of the Irish Universities Act a university:

"Shall promote and facilitate research"

The research alluded to in Art.13 is not specified; therefore one could argue that germ line editing falls under its remit. Furthermore the Irish Medical Council, the regulatory

body for physicians[16], as cited by Akari (2014), is understood to ban germ line editing in its Guide to Professional Conduct and Ethics for Medical Practitioners 8th edt. Chap.47.4:

"You should not participate in creating new forms of life solely for experimental purposes. You must not engage in human reproductive cloning."

The Irish Medical Council does not ban germ line gene editing, as stated by Akari; instead it prohibits reproductive cloning, and somatic cell cloning for the purposes of research. This is one example that illustrates the confusing nature of the human germ line gene editing landscape.

A lack of legislation and a heavy reliance on professional regulatory and institutional bodies is creating an air of legal uncertainty around research on gene editing. Examining Akari's (2014) paper, the regulatory attitude of most countries worldwide is that "gene modification" is banned and, or ambiguous. Countries such as Ireland, The USA, Iceland, and Greece are ambiguous in terms of their regulatory attitude towards gene editing, as the paper cites and interprets the relevant regulations and guidelines available in each individual country. Countries such as Germany, and Italy, however, have a much more definitive stance on the use of germ line editing, as can be seen in their governmental legislation.

[16] It is important to note that only medical practitioners are bound to the IMC's Code of Conduct, meaning scientists could practice against the code.

Germany's Embryo Protection Act (1990) states in Section 5 "Alteration of human germ line cells"

(1) Anyone who artificially alters the genetic information of a human germ line cell will be punished with imprisonment up to five years or a fine.
(2) Likewise anyone will be punished who uses a human germ cell with artificially altered genetic information for fertilisation.
(3) Any attempt is punishable.

Similar to Germany, is Italy's Assisted Medical Procreation Law (2004), where in Chapter VI, Art. 13(b) "Experimentation on human embryos" it states:

"Any form of eugenic selection for the purpose of gametes or embryos and interventions that, through breeding techniques, handling or otherwise using artificial processes, are intended to alter the genetic heritage of the embryo or gamete or to predetermine genetic characteristics, except assistance with diagnostic and therapeutic purposes…"

The clear ban on human germ line editing in Germany and Italy, while wholly restrictive and unaccommodating for scientists wishing to use gene-editing research for the betterment of society, at least provides the medical and scientific community, as well as the citizens of that country, with a very definitive governmental stance towards gene editing in the germ line context.

Moving away from ambiguity, and an outright ban on germ line editing, we reach The United Kingdom (UK). The Human Fertilisation and Embryology Authority (HFEA) was established under the Human Fertilisation and Embryology Act 1990, in response to the Warnock Report of 1984 which recommended the creation of a body to regulate human embryo research and assisted reproduction treatment. As the competent authority, the HFEA covers all aspects of generating human embryos outside of the body, and would therefore include germ line gene editing procedures. The HFEA is a prime example of how creating a competent authority in the field of human fertilisation and embryology can bring about adequate legal and regulatory infrastructure, through public consultation and scientific review. This process is neatly captured in the legislating for mitochondrial donation, which is a limited yet authorised and legislated for human germ line gene editing procedure to remove an impairment from the human germ line.

The HFEA set out in 2011 to open a dialogue with parliament to assess the scientific plausibility of methods to avoid mitochondrial disease. Hence the HFEA established a panel of multidisciplinary experts to summarise and collate information on the scientific methods available to treat mitochondrial diseases. Subsequent to the initial report the HFEA, in 2012, entered into a lengthy public consultation. The structure of these public consultations was inclusive of the majority of stakeholders, and included: (i) deliberative public workshops, (ii) public representative surveys, (iii) open consultation questionnaires, (iv) open consultation meetings, and (v) patient

focus groups. Indeed, it was Jane Ellison MP, who highlighted in parliament the relationship between the government and the specific function of the HFEA (Ellison 2014):

"The Government have run a comprehensive and transparent process over the lifetime of this Parliament to review the public acceptability of mitochondrial donation and the ongoing evidence of safety and efficacy of the new techniques involved. In developing the draft regulations, we have taken extensive advice from the scientific and research community and the United Kingdom's regulator, the Human Fertilisation and Embryology Authority (HFEA)."

In total three separate reviews were undertaken by the HFEA at the request of government, all of which had slightly differing terms of reference. Subsequently, the UK parliament created a statutory instrument (S.I. 2015 Number 502: The Human Fertilisation and Embryology (Mitochondrial Donation) Regulations 2015) to be incorporated into the Human Fertilisation and Embryology Act 1990 (as amended by the Human Fertilisation and Embryology Act 2008). Therefore, the role of the HFEA was crucial in bridging the legislation in Parliament with the sentiments of the scientific community and the general public.

Looking to the UK and the HFEA it would, in my opinion, seem reasonable for to utilise their competent authorities in order to engage the public and liaise with Parliament on issues concerning germ line gene editing. This may be achievable within

the framework of an international code of conduct. This code would be enacted by member states that wish to use germ line gene editing. As such, states utilising human germ line gene editing will be doing so together under a shared code of conduct. Meanwhile the states not implementing germ line gene editing can still utilise the subsidiarity principle, meaning their political decisions regarding germ line gene editing will remain local, and will not be dictated by an over arching international institution or policy. As Indira Nath, of the All India Institute of Medical Sciences, remarked at the International Summit on Human Gene Editing 2015 (Committee on Science, Law et al. 2016):

"Governance regarding technologies is now crossing geographical borders, and with national policies becoming rapidly transnational, one would say that governance is no longer just local, but is becoming a network of nations working together."

5.3 Regulatory Bodies and Governance

There is a changing global regulatory framework in relation to medical research, where international treaties are becoming obsolete, and systems of "soft law" are replacing "hard law," Committee on Science, Law et al. (2016). It is increasingly difficult to take into consideration multi-national ideas and beliefs and reflect them in one single rule or law (hard law), hence the move to systems of soft law. Soft law regulation of CRISPR mediated germ line gene editing would therefore reflect an expectation as enshrined in an international code of conduct. Naturally, the movement from hard to

soft law in relation to gene editing has its critics regarding its enforceability[17] and its inability to deter people straying from the letter of the law.

Many scientific and regulatory bodies are currently informing governance regarding gene editing. Of note are the statements released by: (i) The Wellcome Trust, (ii) The Hixton Group, and (iii) The Council of Europe. The Wellcome Trust released a joint statement concerning the role of germ line gene editing in the context of UK law. The Wellcome Trust recognises that gene editing is a powerful technology that has a great capacity for the improvement of human health, and stresses the need for active early public engagement in the issue. Moreover, the Wellcome Trust highlights the necessity for a regulatory framework for gene editing:

"…demarcating research use of genome editing from potential clinical use, and carefully distinguishing use of somatic and germ cells, will ensure that the research community remains at the forefront of this novel area…"

The Hixton Group – An International Consortium on Stem Cells, Ethics, and Law, released a more in-depth statement concerning germ line gene editing. The sentiments of The Hixton Group's statement reflect those expressed in the Wellcome Trust's,

[17] Sanctions are difficult to impose in the scientific research setting as one of the main modes of punishment would be to cut funding to the research laboratory, however given the relative low cost of CRISPR, monetary sanctions may not be as deterring as once thought.

however the Hixton Group statement elaborates on points such as, developing a "flexible roadmap" to allow scientific research to continue without being needlessly constrained, and the need for "oversight structures" which audit and license scientific institutions. Finally, the Council of Europe – Committee on Bioethics released a statement in December of 2015, which refers the reader back to a previous convention held by the Council - Convention on Human Rights and Biomedicine (ETS N° 164, 1997), otherwise known as the Oviedo Convention. The statement references Art.13 of the Oviedo Convention, which even though written in 1997 is still profoundly applicable today:

"An intervention seeking to modify the human genome may only be undertaken for preventive, diagnostic or therapeutic purposes and only if its aim is not to introduce any modification in the genome of any descendants."

A common thread throughout all the above listed statements, and many others similar to these three, is that they all call for significant debate not just within the scientific community but also within the public domain. Furthermore, they all recognise at varying levels that there is a need for some regulatory framework to govern the research involving germ line editing. While the mode of governance is not explicit, many commentators believe that if there was a shared international code of conduct, similar to what happened with The Asilmoar Conference in 1975 in response to fears relating to genetic engineering, then a lot of legal unrest could be quelled.

5.3.1 Asilomar 1975, and Washington 2015

The Asilomar Conference on Recombinant DNA (Berg, Baltimore et al. 1975) was made up of a multidisciplinary cohort of people, to draw up guidelines concerning the use of a new biological technology termed recombinant DNA technology. The conference has been described as a significant milestone in how the scientific community bridged their discussions with the general public. In essence, the conference set a precedent in showing that the way to go about responding to a new scientific breakthrough was to develop guidelines on how to regulate the new technique. Such guidelines reassured the scientists using the technique of their experimental remit, while the guidelines also reassured the otherwise apprehensive and public.

In the context of germ line gene editing commentators believe that an Asilomar styled conference would have the same regulatory, and reassuring effects. Indeed, Moreno states (Bosley, Botchan et al. 2015):

"There's a nearly reflexive tendency to think of Asilomar…"

However, the scientific landscape has changed considerably since the days of Asilomar. An international summit was held in Washington in 2015 (Committee on Science, Law et al. 2016) to discuss human germ line gene editing, and it is rather striking the difference between the Washington summit and the Asilomar conference. The key

difference between Washington, and Asilomar was their audiences. Asilomar was designed for scientists, and more specifically a subsection of scientists who were working in the field of gene editing at that time, however the audience at Washington was filled with people from an array of academic disciplines such as scientists, ethicits, philosophers etc.

As mentioned, at the time of the Asilomar, techniques like gene editing were only available to a minority of research laboratories throughout the United States, furthermore the number of research laboratories in general were far fewer. Fast forward to the scientific landscape of 2016, and the accessibility of gene editing techniques are not only open to the vast majority of scientists with varying financial support, but also to members of the public (previously referred to as biohackers in Chapter 4). However one quality that is still much needed in today's gene editing debate, that was evident in Asilomar, was the quality of leadership. Leadership needs to be taken by an entity to begin the process of engaging the scientific community and the general population in a dialogue on gene editing, and how to regulate scientific and non-scientific use of a gene editing technology such as CRISPR. Commentators point to the framework and quality of debate and leadership shown throughout the course of the mitochondrial DNA transfer debate. While the context of ethical and legal issues surrounding the mitochondrial DNA debate are different to those of germ line gene editing, it is the framwork and the manner in which the debate was conducted that is of most importance going forward.

As the issue of germ line gene editing is a global one, commentators (Bosley, botchan et al. 2015) have suggested that the most logical way forward would be to have national oversight, but said nation would subscribe to an over arching international set of guidelines. These international guidelines could at least reflect a concensus of opinions from its signatories, thus providing an amicable construct for nations to apply to their own policies or legislature in accordance with their community values. Coming full circle, we now reach a point whereby many countries do not have a system or a body in place to effect the national oversight, hence it is imperative that countries take note of the HFEA model in the UK going forward.

5.4 Proposed Models of Regulation

As can be inferred from the preceeding sections, regulation of gene editing is the only plausible way forward to effect meaningful governance. Evitt, Mascharak et al. (2015) cite four approaches to national oversight: (i) laissez-faire (ii) an international ban, (iii) a temporary moratorium, and (iv) regulation.

5.4.1 Laissez-Faire

The concept of a laissez-faire regulatory approach towards gene editing is particularly difficult to envisage given the huge ramifiations gene editing presents for preventative medicine, and indeed for the development of the human species. The concept of laissez-faire would see governments and regulatory bodies divest themselves of responsibility and would therefore allow gene editing to take its course within society without legal interference. Laissez-Faire is a somewhat fanciful ideology

whereby one could argue that gene editing, including germ line gene editing, should be allowed to go ahead unimpeded by regulation as the technique seeks to, some degree, evolve the human species. However, it is the opinion of many commentators including my own, that the risk to human species, which would inevitably rear its head through the practice of eugenics for genotypic as well as phenotypic traits, is far too great to leave unregulated. Furthermore, this approach is not adopted for any other medical technology, and one only needs to view the strict regualtions within the EU concerning clinical trials, and medical devices.

5.4.2 International Ban

From the extreme of a laissez-faire attitude, the opposite end of the spectrum would be to enforce an international ban on germ line gene editing. Similar to the laissez-faire model, an international ban is not plausible given impracticalities in policing the ban. Not only would scientists have to be policed, but so too would the general public given the presence of biohackers. A further disadvantage of implementing an international ban would be that no furhter research could be carried out on the germ line which could have significant implications in how we view and, in some cases, treat impairment.

5.4.3 Temporary Moratorium

Currently a temporary moratorium is the approach being utilised, however unlike laissez-faire and an international ban, the temporary moratorium seems to be creating an air of ethical and legal uncertainty. Ideally, the moratorium should be used

to foster discussion among the scientific community and the general public, and not as framework to halt scientific research indefinitely, as the task of having to regulate for gene editing is seen to be too onerous. Should the international community believe that a temporary moratorium is the best approach in the meantime there needs to be strict conditions attached in case the moratorium; evolves into a prohibition, or drives the technology underground, or pushes people to partake in therapy tourism to regions where regulation is less controlled.

5.4.4 Regulation

As Evitt, Mascharak et al. (2015) point out, regulating for gene editing is the only logical and sustainable approach. Evident throughout the course of this chapter, and reflected in Evitt's article, is the need to set up a body with national oversight of gene editing, which is accountable to an overarching international body. While the intricacies on how to specifically regulate gene editing in a national context have yet to be developed, Evitt, Mascharak et al. do provide suggestions such as implementing financial and regulatory checkpoints at varying stages of a gene editing clinical trials. Regulations are currently speculative, and will only come about once there are a growing number of countries seeking to utilise human germ line gene editing. The idea of a broad consensus among countries may seem like an intuitive way forward, however many countries who are opposed to germ line gene editing would oppose such a consensus. Therefore, another way forward may be for the countries interested in using germ line gene editing, could agree a shared code of conduct which can be

incorporated into national legislature. This method would, at least, harmonise the applications of germ line gene editing in those countries using the technology, and would not encroach on the autonomy of nations unwilling to implement germ line gene editing.

6. Conclusion

Using the BMA Eclectic method, I have aimed to elucidate the key ethical and legal questions, with supporting analyses of community values and clinical evidence, regarding CRISPR gene editing technology.

6.1 Clinical Evidence

The clinical evidence supporting CRISPR gene editing technology is plentiful in the non-clinical, and clinical somatic platforms. CRISPR is most widely used today in the non-clinical setting through research involving cell lines, and microbes. As previously mentioned, commentators have cited that the clinical somatic platform will be the platform that will thrive, given the accessibility to source material. CRISPR in the somatic context, has the power to revolutionise how impairments are treated through developing engineered cellular therapies. Moreover, given the usability of CRISPR, amateur scientists, or biohackers, are currently able to use CRISPR for trivial tasks, such as engineering yeast for brewing beer, in community labs.

The current evidence for CRISPR technology on the human germ line is rare. Liang's (2015) paper was released, and was the cause of considerable ethical controversy. Nonetheless, the clinical evidence that this paper provides highlights that editing the human germ line is, by no, means an easy feat. The experiments were plagued by off target mutations, and crucially the number of embryos used was not

enough to provide a wide scale picture CRISPR's capabilities. To conclude, the clinical evidence is most prevalent in the non-clinical, and the clinical somatic platforms, and it has been documented that these are the two platforms that have the potential to truly change the face of modern medicine, in a relatively short time frame. Germ line gene editing, on the other hand, is still in its infancy, meaning there is very little evidence to support its clinical efficacy. However, through the germ line experiments, there were some embryos that underwent the gene editing as had been planned. It therefore stands, that with an increase in research, will come a refinement in the technique. Germ line gene editing, while not on the immediate horizon in comparison to the to other two platforms, has the capacity to overwhelmingly change the medical landscape for future generations.

6.2 Community Values

Analysing the philosophies and models of impairment, in my opinion, highlights the fact that Two-Tier Naturalism and Constructivism are the two key philosophies to implement in this discussion on gene editing. Impairment, as previously described, is an umbrella term, broken down, by some, into disease and disability. I believe, differentiating between what one classifies as a disease, and a disability proves to be particularly difficult, moreover futile when applied to the gene editing debate. Unlike simple naturalism, Boorsian naturalism, and the models of disability, Two-Tier

Naturalism, and Constructivism serve, in my opinion, as the best models to analyse the spectrum of impairments, and how they inform the debate on gene editing.

Two-Tier Naturalism is an extension of simple naturalism, and is a robust framework used to understand impairments, as manifestations of suffering as a direct result of an abnormal biological process. Elaboration on the suffering referenced in the Two-Tier Naturalism framework is not expanded, meaning suffering can be innate, or experienced. Innately, impairments cause physiological and psychological suffering given the very nature of the impairment. Experiential suffering, can be experienced through the stresses of interacting with one's environment with an impairment, while one may suffer psychologically due to the fact that they are physiologically unable to preform a task. As mentioned, Two-Tier Naturalism does not differentiate between the sufferings experienced, so long as it is present. Constructivism, on the other hand, gives a great deal of power to value judgements and how they apply to impairments. Constructivism, unlike the other philosophies and models (bar the social model of disability) is not empirical when defining impairments. Instead constructivism, allows the user to create a landscape where impairment is judged in relation to the ideals and values held culturally, and societally. Two-Tier Naturalism and Constructivism can be applied to many impairments in isolation, however one does not need to be a strict Naturalist nor Constructivist when interpreting impairments.

Moving forward with Two-Tier Naturalism and Constructivism our collective ideas and requirements for what are deemed as impairments are challenged. Today, it could be argued that, cancer has many abnormal biological pathways and, in most cases, is associated with a degree of suffering. The conditions for impairment as per Two-Tier Naturalism are satisfied given the presence of a biological abnormality, and the presence of suffering, furthermore the conditions of Constructivism may be satisfied should the suffering associated with cancer be disvalued by society. However, one could argue that substituting the impairment from cancer to obesity, or ugliness, or deafness, or Down Syndrome etc., would yield the same results if the conditions of the philosophies are in some way met. While, it would seem, that any biological trait exhibited by a cohort of people could be deemed an impairment, should there be enough of a societal and cultural belief that said trait is an impairment, it should also be noted that it is only now that there is a potential medical modality to begin the removal of said "impairment" from the human species via the germ line. Two-Tier Naturalism and Constructivism, therefore, serve as frameworks for identifying impairments, however it is the discipline of applied ethics that provides a degree of proportionality.

6.3 Ethics

The ethics of gene editing, as mentioned previously, is informed by community values. Gene editing is applied to three key platforms, non-clinical, clinical somatic, and clinical germ line, however it is the clinical germ line platform where the majority of

ethical concerns are raised, and is also the platform in which community values will inform the most. Particular attention was given to the principles of: beneficence, maleficence, autonomy, and justice.

The non-clinical platform, while not without its ethical concerns, as mentioned previously, falls out of the scope of this piece. The clinical somatic platform, however serves an exciting ground for gene editing research, and according to many commentators is the platform that will be the first to be implemented clinically. As discussed, the clinical somatic platform's ethical hurdles are; how a gene edited somatic cell therapy should be trialled, and secondly, who has access to the gene editing technology. It is my belief, that the clinical somatic platform imparts the most tangible beneficence out of the three platforms. Gene edited somatic cell therapies can be viewed in the same light as any other medical modality that seeks to treat an impairment. As such, a degree of harm may be encountered either through trialling of the therapy, or as a side effect of the therapy once licenced, however the degree of beneficence is overriding. Furthermore, and most crucially, the treatment of impairment with a gene edited somatic cell therapy does not remove the heritability of said impairment from the genome of the affected individual. While the potential beneficence of the gene edited somatic cell therapies is great, there remains a maleficent aspect to the platform. The accessibility of the technology and to source material means that gene editing technology is open to a much wider audience, other than scientists, and is therefore open to neglect and abuse.

As previously described, the clinical germ line platform is the platform that raises the most ethical and legal concerns, and, as described, the philosophical constructs, Two-Tier Naturalism and Constructivism, inform our debate on gene editing as a whole. The key distinction, however, between the somatic cell platform, and the germ line platform, is the issue of heritability. In the germ line context impairments can be removed from the individual and from successive generations. Therefore, while today society may deem it acceptable to edit cancer causing genes out of the human germ line with the backing of the philosophical frameworks, society may also consider it acceptable, at a later point, to edit out genes associated with ugliness, should the same criteria for the frameworks be satisfied. It is, therefore, the role of ethicists to provide a degree of proportionality to the debate of germ line gene editing. Unfortunately, proportionality may upset and, may not appease many, however it is the role of ethicists to draw a line regarding the gene based impairments that could potentially be edited out of human existence. These impairments, I argue, should be selected based on the collective intentions of the society proposing the editing. It is understandable to want to edit out genes associated with life threatening, or life limiting impairments should there be a potential for a high degree of suffering. However, it is also understandable that superficial biological traits may be deemed unsuitable for germ line gene editing, as the intention is to remove something that is simply disvalued rather than to remove a trait that has an innate ability to manifest itself in suffering.

Once a germ line gene-editing regime is in place, there still remains ethical concerns regarding patient autonomy, and justice. The difficulty germ line gene editing encounters with autonomy is, as previously mentioned, the dichotomy between an individual autonomy, and a species autonomy. Should a germ line editing regime be in place, and a prospective parent not wish to partake in the removal of certain authorised genes from their embryo, are these parents acting in the best interests of their future child, and in the best interests of the human species? Furthermore, the ethical issues concerning the principle of justice, may see the above mentioned parent being unable to even access the germ line gene editing technique, on account of their inability to pay. Therefore, germ line gene editing may only be the preserve of the wealthy, and as such would force people of lower socio-economic classes to lead an unedited life. Or indeed, for the more dystopian reader, should the ability to pay not be a mitigating factor, may result in people being forced to lead edited lives.

Moving away from germ line gene editing for impairments, editing the germ line for purposes of enhancement is reached. While the concept of enhancement is not as prevalent as editing out impairment, enhancement is none the less a cause for ethical concern. Enhancement, I believe, in the germ line gene editing platform is a kin to the proverbial “can of worms.” Enhancement, seeks to make an individual realise their “full potential” through editing the genome in such a manner that provides a genetic advantage to that individual within their environment. However, it is my opinion, that

enhancement will turn out to be a folly, or fashion, as there is no way to discern when the individual has fully reached their "full potential."

6.4 Law

The legal and regulatory status of gene editing, while permissible in the non-clinical, and clinical somatic platforms given it's inoffensive subject material, is in the germ line platform restrictive and lacking. The regulatory landscape regarding germ line gene editing has created an air of uncertainty among the scientific community and, unlike the Asilomar conference, international summits are doing little to provide a gold standard framework, simply due to the contentious subject material, and the accessibility of the technology to scientists, and biohackers alike. In my opinion, laws and regulations regarding germ line gene editing can only be regulated for on a national level, but said nations should at least commit to a basal level of over arching regulations as set out by an international organisation. Such over arching regulations should be broad in scope, and would encompass the collective desires of nations who wish, and do not wish to partake in germ line editing research. Germ line gene editing, can in my opinion, only be regulated through a national regulatory body, which alongside government, are signatories to a shared international "code of conduct" or form of agreement that defines how and under what circumstances germ line gene editing should ideally be conducted.

6.5 Going Forward

In closing this piece, and in going forward with gene editing on the horizon in three distinct platforms, it is of paramount importance that adequate scientific, social, ethical, and legal discussion is undertaken. Science cannot be the preserve of scientists, particularly when their work could have such tangible effects to humanity, in the way that germ line gene editing possesses. I believe that research using gene editing techniques in the non-clinical, and the clinical somatic platforms should be encouraged to continue, however, I believe that it would be prudent to continue with a moratorium on germ line gene editing. This moratorium must be subject to strict conditions regarding duration, and the interim period must be used to facilitate national and international discussion on a lay, and scientific level. It is my belief that the scientific community should not begin research on the germ line with the intention of using the research to remove impairment from the genome, as I believe, that there is currently not sufficient knowledge regarding basic genomics, and gene interplay in modes of normality and impairment.

I would recommend, a stepwise approach to germ line gene editing. Firstly increasing funding into basic gene science should occur, to gain a deeper understanding into how the human genome functions normally. Secondly, research into the impairment of interest should occur, so that there is sufficient knowledge to map the genes of interest in the abnormal pathways. Thirdly, with the supporting

knowledge from steps one, and two, applying germ line gene editing to developing embryos to study the genetic pathways of the impairment *in vivo* should occur. Finally after extensive laboratory trials, long-term clinical trials may be initiated if the research is sound. Thereafter, I would be in favour of implementing germ line gene editing; only under the conditions that the aforementioned ethical discourse has been held, and that there is adequate national legislation, an over arching international agreement, and that there has been significant, robust, and meaningful national debate among all stakeholders, in conjunction with superb clinical evidence.

To close, the potential applications of gene-editing technology are vast, and pose significant philosophical, ethical and legal concerns regarding our interpretations of impairments, and subsequently their treatment. Going forward, it would seem that gene editing is our vehicle into a brave new world.

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