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CRISPR-mediated human germline editing: Benefits, risks, and why a ban is unethical

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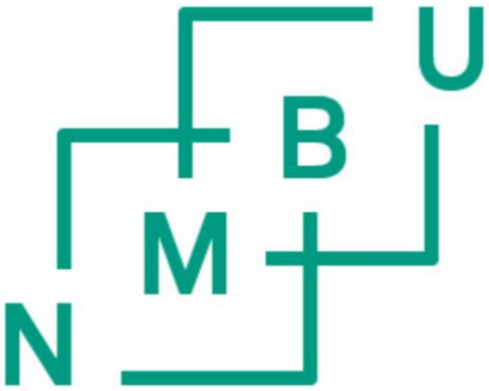

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It is a strange fancy to suppose that science can bring reason to an irrational world when all it can ever do is give another twist to a normal madness

– John N. Grey, *Straw Dogs: Thought on Humans and Other Animals*

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ABSTRACT

CRISPR/Cas gene technology provides a versatile system for site-specific gene editing in virtually any cell and has made it possible to cure and prevent genetic diseases and defects. Many genetic diseases, such as Tay Sachs and Huntington's disease, cause horrendous suffering and premature death, and treatment options are often inefficient or non-existent. Correction of the disease-causing mutation in the germline will save both the affected individual and subsequent generations from the harm of genetic disease. There are still some technological challenges and risks that must be surmounted before CRISPR/Cas gene technology can be adopted for clinical applications. Still, given the tremendous benefits, it may be acceptable to proceed to clinical trials even if some risks remain unresolved.

Safety is far from the only concern. Heritable germline editing gives rise to a wide variety of ethical issues, especially with regards to non-medical genetic interventions. The potential to genetically enhance human capacities has raised both excitement and fear, and although some commentators advocates for the potential benefits of human enhancement, it is generally frowned upon. Germline editing for medical purposes is, on the other hand, often viewed as morally acceptable and has even been suggested to be a moral imperative. The problem is that the line between therapy and human enhancement is challenging to define. It is, however, possible to draw a line between therapy and human enhancement. This line can, for instance, be drawn at normal gene function, where correction of a mutated gene to restore the gene's normal function is therapy, whereas edits in genes where there is no mutation to be corrected are human enhancement.

Therapeutic germline editing is nevertheless often discussed either on the premise that there is no distinction between therapy and human enhancement or on the premise that allowing therapeutic germline editing will inevitably lead to allowing human enhancement. The risk is that the benefits of therapeutic germline editing are being overshadowed by the much more disputed potential to enhance human capacities and thus opt for a ban on human heritable germline editing. It is, however, questionable whether a ban on germline editing can be justified given the tremendous benefits.

The aim of this thesis is to analyze whether it is morally permissible to prohibit germline editing, especially considering the potential to cure and prevent genetic diseases. Some of the most prominent ethical issues with allowing germline editing (such as the slippery slope argument, eugenics, discrimination, increased inequality, and violation of the child's right to

an open future) are discussed, but neither of these concerns is sufficient to justify a ban. The thesis concludes that it is not only ethically justifiable to permit germline editing but a moral imperative to continue the research and eventually proceed to clinical trials if the technology is confirmed to be sufficiently safe.

SAMMENDRAG

CRISPR/Cas genteknologi er et allsidig system for spesifikk redigering av gener i hvilke som helst celler, blant annet for å korrigere genmutasjoner som forårsaker sykdom. Mange genetiske sykdommer, slik som Tay-Sachs og Huntington's sykdom, forårsaker alvorlig lidelse og prematur død, og behandlingsalternativene er ofte ikke-eksisterende eller lite effektive. Korrigering av sykdomsgivende mutasjon i kjønnsceller eller embryoer vil være arvelig og vil dermed forhindre sykdommen i både det aktuelle (fremtidige) individet og dets avkom. Det er noen teknologiske utfordringer og risikoer som må løses før teknologien kan tas i bruk. Enkelte av sykdommene teknologien kan forhindre er imidlertid så alvorlige at det kan være aktuelt å starte klinisk testing til tross for noe risiko for negative virkninger.

Hvorvidt genredigering er trygt er imidlertid langt fra den eneste bekymringen. Arvelig genredigering av mennesker reiser en rekke etiske problemstillinger, spesielt når gjelder genredigering som ikke er medisinsk begrunnet. Mulighetene til å redigere gener med hensikt om å 'forbedre' menneskers egenskaper som intelligens, fysikk, forventet levealder, osv. vekker både begeistring og frykt. Til tross for at mange kommentatorer anerkjenner at menneskelig forbedring ('human enhancement') kan ha stor nytteverdi er de aller fleste enig om at det er uetisk og at det derfor bør unngås. Til forskjell er genredigering med hensikt om å kurere og forhindre alvorlig sykdom mer akseptert, og noen vil til og med påstå at det er et moralsk imperativ. Det faktum at grensen mellom medisinsk behandling og menneskelig forbedring er vanskelig å definere gjør det imidlertid utfordrende å tillate genredigering for medisinske årsaker og samtidig forby menneskelig forbedring. Det er imidlertid mulig å skille mellom behandling og forbedring ved å for eksempel se på normal genfunksjon. Ved å sette grensen basert på hva som er den normale funksjonen til det aktuelle genet vil korrigering av mutasjoner for å gjenopprette genets funksjon være behandling, mens endringer i gener hvor det ikke er noen mutasjon å korrigere vil være menneskelig forbedring.

Til tross for at det er mulig å sette en grense mellom behandling og forbedring blir begge formålene ofte diskutert på samme premisser. Dette skyldes ofte manglende anerkjennelse av at grensen kan defineres og delvis tanken om at ved å akseptere medisinsk genredigering vil forplikte oss til å også tillate menneskelig forbedring (skråplansargumentet). Fokuset i debatten om genredigering blir derfor ofte lagt på de etiske problemstillingene ved å forbedre menneskers egenskaper. Den store nytteverdien av medisinsk genredigering risikerer dermed å bli overskygget av frykten for såkalte 'designer babyer'. Dette kan skape et inntrykk av at den

beste (og enkleste) løsningen vil være å motsette seg alle typer genredigering og man risikerer dermed å forby en teknologi på feilaktig grunnlag. Den store nytteverdien av genteknologi gjør imidlertid et forbud vanskelig å forsvare.

Målet med denne oppgaven er å analysere hvorvidt det er etisk riktig å forby arvelig genredigering, spesielt med tanke på potensialet for å kunne kurere og forhindre genetisk sykdom. Oppgaven tar for seg noen av de mest fremtredende etiske problemstillingene ved genredigering (slik som skråplansargumentet, eugenikk, barnets rett til en åpen fremtid, økt ulikhet og diskriminering) og viser at ingen av disse argumentene gir tilstrekkelig grunnlag for å forby genredigering. Oppgaven konkluderer med at det er et moralsk imperativ å fortsette forskningen og begynne med kliniske studier når det er bekreftet at teknologien er tilstrekkelig trygg.

ABBREVIATIONS

Cas	CRISPR associated
CRISPR	Clustered regularly interspaced short palindromic repeats
crRNA	CRISPR RNA
dCas9	Dead Cas9
DSBs	Double stranded DNA breaks
dsDNA	Double-stranded DNA
ESCs	Embryonic stem cells
gRNA	Guide RNA (tracrRNA:crRNA or sgRNA)
HDR	Homology direct repair
HHGE	Heritable human gene editing
iPSCs	Induced pluripotent stem cells
NHEJ	Non-homologous end joining
NHP	Non-human primate
NUC lobe	Nuclease lobe
PAM	Protospacer adjacent motif
PGT	Preimplantation genetic testing
REC lobe	Recognition lobe
RNPs	Ribonucleoproteins
sgRNA	Single-guide DNA
ssODNs	Single-stranded oligo DNA nucleotides
TALENs	Transcription activator-like effector nucleases
tracrRNA	Trans-activating CRISPR RNA
ZNFs	Zinc finger nucleases

GLOSSARY

Cas1 (CRISPR-associated protein 1): Endonuclease. Essential for acquisition of spacer. *See Cas1-Cas2 adaption module*.

Cas2 (CRISPR-associated protein 2): Endonuclease. Essential for acquisition of spacer. *See Cas1-Cas2 adaption module*.

Cas1-Cas2 adaption module: Heterohexameric complex consisting of two Cas1 dimers and one Cas2 dimer. Conserved in the vast majority of CRISPR systems. Responsible for acquisition of spacers from invading phages or plasmids.

Cas9 (CRISPR associated protein 9): RNA-guided effector nuclease in type II CRISPR systems. Generate blunt-ended breaks in dsDNA. Cas9 is inactive when unbound to RNA. Assemble with guide RNA to form an active Cas9-gRNA surveillance complex for target recognition and cleavage. Essential functions in all three stages of antiviral immunity: (1) selection of spacer during acquisition of new spacer; (2) participates in maturation of crRNA during expression and maturation; (3) Cleave target DNA during DNA interference.

CRISPR array: Stores the immunological memory (spacers). Consist of repeating sequences (repeats) interspersed by highly variable spacer sequences. Transcribed into pre-crRNA.

CRISPR vs. CRISPR technology: CRISPR refer to the CRISPR system in general, whereas CRISPR technology refer to CRISPR as a gene editing technology.

crRNA (CRISPR RNA): Maturation and processing of pre-crRNA creates mature crRNA. Contains a 20 nt guide sequence (spacer sequence) for target recognition and parts of the repeat sequence. Form a dual RNA hybrid with tracrRNA (tracrRNA:crRNA) to guide Cas9 to target sequence. *See Guide RNA (gRNA)*.

dCas9 (dead Cas9): Catalytically inactive Cas9 due to mutations in residue D10 (RuvC active site) and residue H840 (HNH active site). Binding to DNA inhibit transcription reversibly. Can be utilized to regulate gene expression.

Gene/genome editing or genetic engineering: The introduction of intended and targeted mutations in the genome. May refer to both somatic gene editing and germline genome editing.

Genotype: Refer to an organism's complete set of genes (broad sense) or an organism's variant of a gene (narrow sense). The term is mostly used in its narrow sense in this thesis.

Genotype-phenotype correlations: Describes how gene mutations (genotype) reflects in the phenotype. Phenotype is primarily determined by the genotype but the high influence of environmental factors of phenotype complicated full elucidation of genotype-phenotype correlations.

Germline: The specialized cell lineage in a multicellular organism that pass on the genetic material to succeeding generations.

Germline editing/Heritable gene editing: Gene editing in early-stage embryo, gametes (sperm or egg) or germ cells. These mutations are heritable* and may affect subsequent generations, as opposed to somatic gene editing that solely affect the individual with the altered genes.

* Note that the edits made in the germline are only heritable if it is implanted in a woman's uterus for gestation.

gRNA (guide RNA): tracrRNA:crRNA or sgRNA. Contains a 20 nt guide sequence with complementarity to target sequence. Assemble with Cas9 to form an active Cas9-gRNA surveillance complex. Guides Cas9 to target DNA.

Homologous direct repair (HDR): Double-stranded DNA break (DSB) repair mechanism. Uses DNA template to introduce a specific sequence/mutation at the break site. Essentially preferred for gene correction and knock-in. Occur at a considerably lower frequency than NHEJ in mammalian cells. Active during S and G2 cell cycle phase.

Mosaicism: The presence of two or more different genotypes within one organism. This phenomenon can occur through several mechanisms.

nCas9 (Cas9 nickase): Cas9 with mutation in residue D10 (RuvC active site) or residue H840 (HNH active site). Cut (nicks) one strand of double-stranded DNA.

Non-homologous end joining (NHEJ): Error-prone repair mechanism for double-stranded DNA breaks (DSBs). NHEJ are active during all cell cycle phases and occur at a much higher frequency than HDR in mammalian cells. Typically leads to random indels (insertions or deletions) or substitutions, which often result in gene knock-out. Inappropriate for gene correction and knock-in.

Off-target mutations: Cas-mediated DNA cleavage outside the intended target sequence.

pre-crRNA (precursor CRISPR RNA): Long transcripts of the entire CRISPR array containing all the spacers and repeats. Maturation and processing of pre-crRNA creates mature crRNA. *See crRNA (CRISPR RNA)*

PAM (protospacer adjacent motif): Short sequence (usually 2-5 bp) necessary for distinguishing between self- and non-self nucleic acid. The presence of correct PAM sequence immediately adjacent to target sequence. PAM-sequence vary among Cas9 orthologs: 5′-NGG-3′ for SpCas9; 5′-NNGRRT-3′ for SaCas9.

Repeats: Repeating sequences in CRISPR array. Identical in length (typically 25-55 nt) and sequence within a given genome.

Seed sequence: 10-12 PAM proximal nucleotides of the guide (spacer) sequence in crRNA. Complementarity between seed sequence and target sequence is especially important for target recognition.

sgRNA (single guide RNA): Artificially engineered guide RNA. Combines tracrRNA and crRNA into a single RNA chimera. Contains a 20 nt guide sequence that can easily be programmed to recognize any sequence. *See Guide RNA (gRNA).*

Spacer: Short sequences from invading phages or plasmid are integrated in the CRISPR array. Provide an immunological memory of previous phage attacks.

tracrRNA (trans-activating CRISPR RNA): Encoded in CRISPR locus but transcribed separately. Partial complementarity with repeat sequence. Essential for crRNA maturation. Interacts with crRNA to form the guide RNA (tracrRNA:crRNA). *See Guide RNA (gRNA).*

TABLE OF CONTENT

LIST OF FIGURES

LIST OF TABLES

CASE STUDIES

CHAPTER 1

INTRODUCTION

Ever since the discovery of DNA as the genetic molecule, the idea of one day being able to make targeted edits in DNA to change the genetic characteristics of human beings has raised both moral concerns and excitement. Human beings' perpetual search for new methods and technologies that will increase our capability to 'control nature' has paid off. The first successful experiment creating a genetically modified bacteria was conducted almost half a century ago, followed by the first genetically modified animal only a year after (Cohen et al., 1973; Jaenisch & Mintz, 1974). Several methods for genetic manipulation have been developed since then. However, it was not until the discovery and development of the powerful RNA-guided gene technology, namely CRISPR, that rapid and efficient genetic modification of human **germline** became a truly achievable prospect.

CRISPR GENE TECHNOLOGY

Clustered regularly interspaced short palindromic repeats (CRISPR)/CRISPR-associated (Cas) systems were first discovered in 1987 when Y. Ishino et al. found an unusual cluster of repetitive DNA units in the genome of *Escherichia coli* (Ishino et al., 1987; Ishino et al., 2018; Nakata et al., 1989). Despite the early discovery of the CRISPR loci, the function of the repetitive units remained undiscovered until the mid-2000s, when F. Mojica and his colleagues suggested a connection between CRISPR and immunity against foreign DNA (Mojica et al., 2005). Infection experiments of *Streptococcus thermophilus* with bacteriophages provided experimental evidence supporting this suggestion (Barrangou et al., 2007). It is now clear that CRISPR/Cas systems in bacteria and archaea confer a complex mechanism for adaptive immunity against viruses (bacteriophages, or phages for short) and plasmids (Brouns et al., 2008; Deveau et al., 2008). Acquisition of immunity occurs by using parts of the invader's genome to integrate a small DNA sequence (called **spacer**) into the bacterial/archaeal genome. The integrated spacer provides an immunological memory that, together with the CRISPR-associated (Cas) nuclease proteins, confer resistance to the invader (Gasiunas et al., 2012; Han & She, 2017).

In 2012, Jennifer A. Doudna and Emmanuelle Charpentier developed a versatile tool for site-specific gene editing – a development for which they were awarded the Nobel Prize in Chemistry in 2020 (The Royal Swedish Academy of Sciences, 2020). By designing/ programming a single guide RNA (**sgRNA**) chimera to guide the "genetic scissor" (Cas nuclease protein) to specific sites in DNA, CRISPR/Cas systems introduce site-specific cuts in double-stranded DNA (dsDNA) in virtually all living cells (Jinek et al., 2012). Unlike former gene-editing technologies such as transcription activator-like effector nucleases (TALENs) and zinc finger nucleases (ZNFs), CRISPR/Cas-mediated DNA cleavage is directed to the target site by a programmable RNA rather than by a protein. Both TALENs and ZNFs require tedious protein engineering of two nucleases, which is far more challenging and time-consuming than designing a single RNA molecule (Chandrasegaran & Carroll, 2016). Hence, CRISPR/Cas as a tool for gene editing is more efficient and feasible. CRISPR gene technology has been the subject of extensive research and has shown great promise in numerous fields ranging from the food industry to medical treatment of severe genetic diseases and cancer.

The development of CRISPR/Cas gene technology has opened the door to revolutionizing progress in the realm of genetic diseases. Many genetic diseases cause tremendous suffering, and treatment options are often inefficient or non-existent. CRISPR/Cas technology confers a promising potential to prevent genetic diseases by correcting the disease-causing mutation in germ cells or early-stage embryos (germline editing). Although somatic gene editing can treat some diseases, germline editing is advantageous because it will affect all the cells in the body[1] and is therefore not restricted to diseases affecting only a few cell types. However, considerable challenges regarding efficiency and specificity necessitate further development and comprehensive evaluation before implementing CRISPR/Cas for heritable human gene editing (HHGE). The fact that these genetic mutations can be passed down to subsequent generations gives rise to additional safety and ethical concerns.

The worlds' first CRISPR-babies

In November 2018, the world received the shocking news that the first germline-edited babies were born in China – despite the lack of evidence for CRISPR gene technology being sufficiently safe for clinical trials. Biophysicist He Jiankui allegedly used CRISPR to inactivate

[1] Note that this is true only if the germline editing does not result in genetic mosaicism (which is one of the major technological challenges with CRISPR/Cas germline editing). This is discussed in Chapter 3: Germline editing with CRISPR/Cas9.

the CCR5 gene[2] to create resistance to HIV infection. Whether or not he was successful is unconfirmed. One of the babies is seemingly heterozygote, but tests show no evidence of harm to other genes, according to Jiankui (Marchione, 2018). Jiankui's experiment was condemned by many for failing to work within ethical guidelines and for violating a general global consensus to refrain from heritable genome editing[3]. He Jiankui was later sentenced to three years in prison for "illegal medical practice" (Normile, 2019). Not only did Jiankui put the two babies at considerable risk, but he also jeopardized scientific freedom and future research on genome editing. Scientific freedom is highly contingent on whether scientists can be trusted to follow ethical guidelines. Irresponsible and unethical experiments create fear – and fear of science can breed unfounded constraints that hamper progress.

BIOETHICS

Germline editing is currently banned in most countries, including Norway (Baylis et al., 2020; Bioteknologiloven, 2003, § 6-2). The birth of the two germline-edited babies in China demonstrated the pressing need for comprehensive, globally accepted ethical guidelines. For decades many scientists tended to distance themselves from the moral and ethical issues of their work. They argued that the aim of scientific research should be to understand the laws of nature. Since the laws of nature are unaffected by human reactions and emotions, the social impact of their work was irrelevant for science as such. Science was perceived as neutral and should be free from politics and moral responsibilities. The antecedent conception that separated science from moral responsibility is generally far from reality today. As scientific and technological developments increased our power to control 'nature' – and technologies such as the internet made scientific findings more accessible for the public – the necessity to have an increased interaction between ethics and science became more apparent. Thus, the cornerstone of bioethics is to set guidelines that prevent scientific and technological interventions from

[2] The CCR5 gene encodes the surface protein C-C chemokine receptor type 5. HIV-1 is contingent on this protein to enter the white blood cells. A 32 nt deletion of the CCR5 gene (called CCR5Δ32) results in a truncated CCR5 protein that is not expressed on the cell surface (Gupta & Padh, 2012).

[3] A moratorium on heritable genome editing has been called for by several prominent scientists, including CRISPR pioneer Emmanuelle Charpentier (Lander et al., 2019; Lanphier et al., 2015). Although the request for a global moratorium has received massive support, it has not yet been declared; nevertheless, a survey from 2020 reported that no country explicitly permits heritable genome editing (Baylis et al., 2020). There are some objections to whether a moratorium on germline editing could be justified. Savulescu et al. (2015) have claimed that "research into gene-editing is not an option, it is a moral necessity". Others have proposed that a "self-regulation approach" may be more suitable (Gregorowius et al., 2017; Weintraub, 2019). It is, however, essential to distinguish between germline editing for research purposes and germline editing to initiate pregnancy. A moratorium on heritable genome editing is not necessarily a prohibition of research on germline editing.

spiraling out of control while concurrently ensuring that the guidelines do not opt for total paralysis of scientific research.

Although there has been an increased focus on the ethical implications of scientific research, the persisting line between science and ethics causes a discontinuity in many bioethical debates. This gap is prominent in the gene-editing debate; the ethical concerns raised by scientists tend to be somewhat superficial, whereas the concerns raised by philosophers can be exaggerated to a point where they bear little resemblance to reality. Resulting from this gap is a confused public with fallacious impressions of scientific and technological possibilities, which poses a significant risk of raising irrational fears.

> The danger of bioethics, as for moral philosophy as a whole, is that of widening the gap between art and life still further, of inventing creatures who live only in the pages of philosophy textbooks and medical journals, and whose world bears little resemblance to the world that we actually inhabit. (Elliott, 1999 p. xvi)

The human germline editing debate

The debate on human germline editing is often centered around the consequences of allowing germline editing. The negative effects germline editing may have on individuals, society, and the human species are given much attention, and the fear of unpredicted consequences opt for strict regulation and possibly prohibition. The negative impacts of adverse genetic disease, on the other hand, are often underemphasized. Although thorough considerations of the potential consequences of germline editing are crucially important, the obscurity and conjectural nature of these concerns make them challenging to evaluate. The wide variety of possible applications and the difficulties in distinguishing between medical treatment and human enhancement complicate the debate even further. The technological challenges and risks may be the same[4], but the benefits are incommensurable. Also, potential negative effects on the individual and society are likely to be far less adverse when removing harmful diseases compared to the potential consequences of human enhancement.

A common opinion is that when – or *if* – CRISPR technology becomes safe enough for germline editing, it is permissible 'only when medically necessary'. The problem, however, is that the line between medical treatment and human enhancement is blurry at best. Although most people have an intuitive perception of what a disease is, many will encounter problems

[4] Certain risks (such as pleiotropy and, to some extent, off-target mutations) are specifically related to the targeted gene. See Chapter 3: Germline editing with CRISPR/Cas9.

defining what counts as a disease and what does not. Similar problems arise when trying to define human enhancement; it may seem straightforward at first sight, but the many 'grey area cases' complicate the establishment of a clear definition. Also, the constant change in interpretation of the terms 'disease' and 'human enhancement' complicates the establishment of a clear distinction between medical treatment and human enhancement even further.

Due to this ambiguity, germline editing for medical purposes is often discussed on the same grounds as human enhancement and so-called 'designer babies'[5]. Since germline editing for human enhancement purposes is considered immoral and wrong by most people, germline editing is generally deemed as something we ought not to do. As a result, people with severe genetic diseases are denied their only chance to live without the disadvantages and limitations of severe disease. Even when discussed separately, medical treatment and human enhancement are often entwined by the slippery slope argument saying that allowing germline editing for medical purposes will inevitably lead to impermissible germline editing. Consequentially, the highly beneficial use of CRISPR is rejected in order to prevent CRISPR from being (mis)used for ethically impermissible purposes.

> On the one hand, by editing the defective genes in human embryos, we can let the offspring get rid of the nightmare of pathogenic genes. On the other hand, the feasibility of technical fields will inevitably lead to some people to cross the ethical boundary for genetic enhancement of non-therapeutic properties. As a result, morality is out of orbit, such as 'commercialization of life' and 'instrumentalization of the body' (Zhou et al., 2020)

But is it morally permissible to disallow potentially life-saving medical treatment out of fear that someone might 'cross the ethical boundary'? Germline editing holds the possibility to drastically decrease the incidences of genetic diseases and thereby increase global human health. Genetic diseases are estimated to affect 5-7% of the population worldwide (National Academy of Sciences, 2017; Verma & Puri, 2015). This may sound like a relatively small number, but 7% of the world's population (~7.9 billion) amounts to ~550 million people that will suffer from genetic disease. By reducing the occurrence of genetic disease to 3%, the number of affected individuals will be reduced to ~230 million. In other words, if germline editing can save 2-4%

[5] I use the term 'designer babies' used here because it is highly prevalent in the human germline editing debate, but the term is in some sense fallacious and misleading. I will explain in *Chapter 5:Ethical issues with human germline editing* how heedless use of the term can damage the debate.

of those with a genetic disease, as many as 320 million people from the horrendous fate of genetic disease.

An appropriate approach to establish a regulatory framework for human germline editing should not only consider the potential consequences of allowing germline editing; the consequences of *not* allowing germline editing are of equal importance. CRISPR technology is undeniably powerful and should be used with caution, but can the possibility to misuse CRISPR give sufficient justification to withhold potentially life-saving treatment? Given the immense potential of germline editing for curing horrible diseases, it is questionable whether any reason can justify prohibiting CRISPR technology. Elucidation of the burden of genetic diseases will highlight the beneficence and necessity of germline editing and may provide a more apparent distinction between medical treatment and human enhancement. In that way, the evaluation of germline editing to remove severe diseases will not be clouded by the issues with 'designing' human beings.

THESIS OUTLINE

The aim of this thesis is to analyze whether it is morally impermissible to abstain from human germline editing, particularly in respect of correcting genes responsible for severe and fatal diseases. Essential aspects are discussed systematically and relatively separately in chapters 2–5 before they are combined in chapter 6 to investigate the moral obligations regarding germline editing. In order to investigate whether a ban on human germline editing is morally impermissible, the thesis will focus on the following key questions:

1. Are the ethical issues with human germline editing sufficient to justify a ban on potentially life-saving technology?
2. What are our moral obligations when creating a child?
3. To what extent should parents be allowed to decide what child they want?

The thesis will start with an introduction to the technology in order to answer the key questions in accordance with current scientific research. The basics of CRISPR and its mechanism are presented in *Chapter 2: CRISPR/Cas – The basics*, followed by an introduction to the technological aspects of germline editing in *Chapter 3: Germline editing with CRISPR/Cas9*. The technological challenges and risks with CRISPR/Cas9 technology as it stands today are presented in chapter 3. It is, however, plausible to assume that these challenges

will be surmounted within a reasonable amount of time. The ethical issues in the remaining chapters are therefore discussed on the assumption that germline editing with CRISPR/Cas9 is safe.

The human germline editing debate is a minefield of complicated and often unspecified terminology. The problems with establishing a line between medical treatment and human enhancement are aggravated by the lack of universally accepted definitions for the terms 'disease', 'disability', 'therapy', and 'human enhancement'. To tackle this problem and avoid that confusion with terminology interferes with the ethical discussion, the meaning of the abovementioned terms is addressed in *Chapter 4: Establishing the line between medical treatment and human enhancement*.

Some of the most prevalent ethical concerns regarding human germline editing are discussed in *Chapter 5: The ethical issues of human germline editing* to evaluate whether the ethical issues are sufficient to justify a ban on human germline editing. The discussed concerns include (but are not limited to): the slippery slope argument and the fear of a new eugenic era; the effect it may have on inequality and discrimination; personal identity and freedom to create its own future; and the difficulty with balancing the parents' reproductive autonomy and the child's future autonomy.

As a final point, *Chapter 6: Choices and obligations when creating a child* discusses the degree of obligatoriness and freedom of choice regarding human germline editing. This chapter examines different approaches in the ethical debate on human germline editing in order to evaluate the extent to which human germline editing can be seen as something we owe to the child. Chapter 6 also discusses whether parents are obligated to approve genetic intervention to remove disease or disability, as well as the extent to which parents should be free to choose their offspring's genetic makeup.

The focus of this thesis is the ethical questions regarding human germline editing and will therefore not elaborate on the ethical aspects of the CRISPR technology itself. For the sake of simplicity, the thesis is written on the presumption that the technology is not unethical *in itself*. To claim that a technology is unethical in itself attributes a moral agency to technology that can only exist in the context of human action. Technologies possess neither intention nor free will, so it cannot be held responsible for its actions. Besides, assertions that the technology itself is wrong implicate that every purpose and outcome of using it is bad. CRISPR is a highly versatile technology that can be used for many different purposes, each of which has its own value characteristics (Sundström, 1998). Thus, the value is decided based on intention and purpose

rather than by the technology itself. However, many have rejected the Value-Neutrality Thesis[6], but that debate is beyond the scope of this thesis.

[6] The Value-Neutrality Thesis state that technology is neither good nor bad. See, for example, Miller, B. (2021). Is technology value-neutral?. *Science, Technology, & Human Values*, *46*(1), 53-80.

CHAPTER 2

CRISPR/CAS – THE BASICS

Bacteria are in a constant battle with bacteriophages. As a result, many bacterial species have evolved a variety of complex antiviral defense mechanisms, one of which is the highly adaptive CRISPR immune system. Clustered regularly interspaced short palindromic repeats confer resistance to phages by storing an immunological memory of previous attacks.

The immunological memory is acquired in response to phage attack by integrating a short DNA sequence (**pacer**) into the **CRISPR array** (**Figure 2**) in the bacterial genome. This spacer sequence is complementary to the invading phages genome and – when transcribed and processed to mature CRISPR RNA (**crRNA**) – functions as a guide for recognizing the phage if the bacteria encounter a second attack. The invading phage will then be destroyed by CRISPR-associated (Cas) protein(s). Once the spacer is integrated, it can be passed on to subsequent generations by Lamarckian inheritance (Koonin & Wolf, 2009). Constitutive transcription of Cas proteins and the CRISPR array (Deltcheva et al., 2011; Young et al., 2012) containing the spacer sequences provides rapid detection and silencing of the invader if the bacteria encounter a second attack.

Classification of CRISPR systems

Extensive sequencing of bacterial and archaeal genomes has revealed a wide distribution of diverse CRISPR/Cas systems among bacteria and archaea. One or more CRISPR immune systems have been found in approximately 40–50% and 90% of all analyzed bacterial and archaeal genomes, respectively (Kunin et al., 2007; Makarova et al., 2015).

Owing to the adaptability, i.e., the capability to target virtually any sequence, CRISPR systems are not required to evolve an immense diversity of specificities to provide antiviral immunity (unlike most other immune systems) (Koonin et al., 2017). Nevertheless, phages have developed mechanisms to inhibit CRISPR/Cas systems, creating an evolutionary arms race between the bacterial CRISPR/Cas system and the phage anti-CRISPR system (Maxwell, 2017). Consequently, the evolutionary pressure promotes rapid changes in the CRISPR loci involving numerous rearrangements of the locus architecture and horizontal transfer of

complete loci or individual modules, as well as fast evolution of *cas* genes resulting in broad variability (Koonin et al., 2017; Makarova et al., 2015).

CRISPR/Cas systems are primarily classified into two classes (**Figure 1**), Class 1 and Class 2, based on the character of nuclease (Cas) effector: multi-protein effector complex in Class 1 and single-protein effector in Class 2 (Barman et al., 2019). Each of the two classes is divided into three types: Class 1 systems constitute type I, III, and IV (**Figure 1a**); Class 2 systems constitute type II, V, and VI (**Figure 1b**). Furthermore, the six types are classified into, thus far, 33 distinct subtypes (Koonin et al., 2017). Due to the absence of universal *cas* genes and the frequent modular recombination, classification into subtypes requires a multipronged

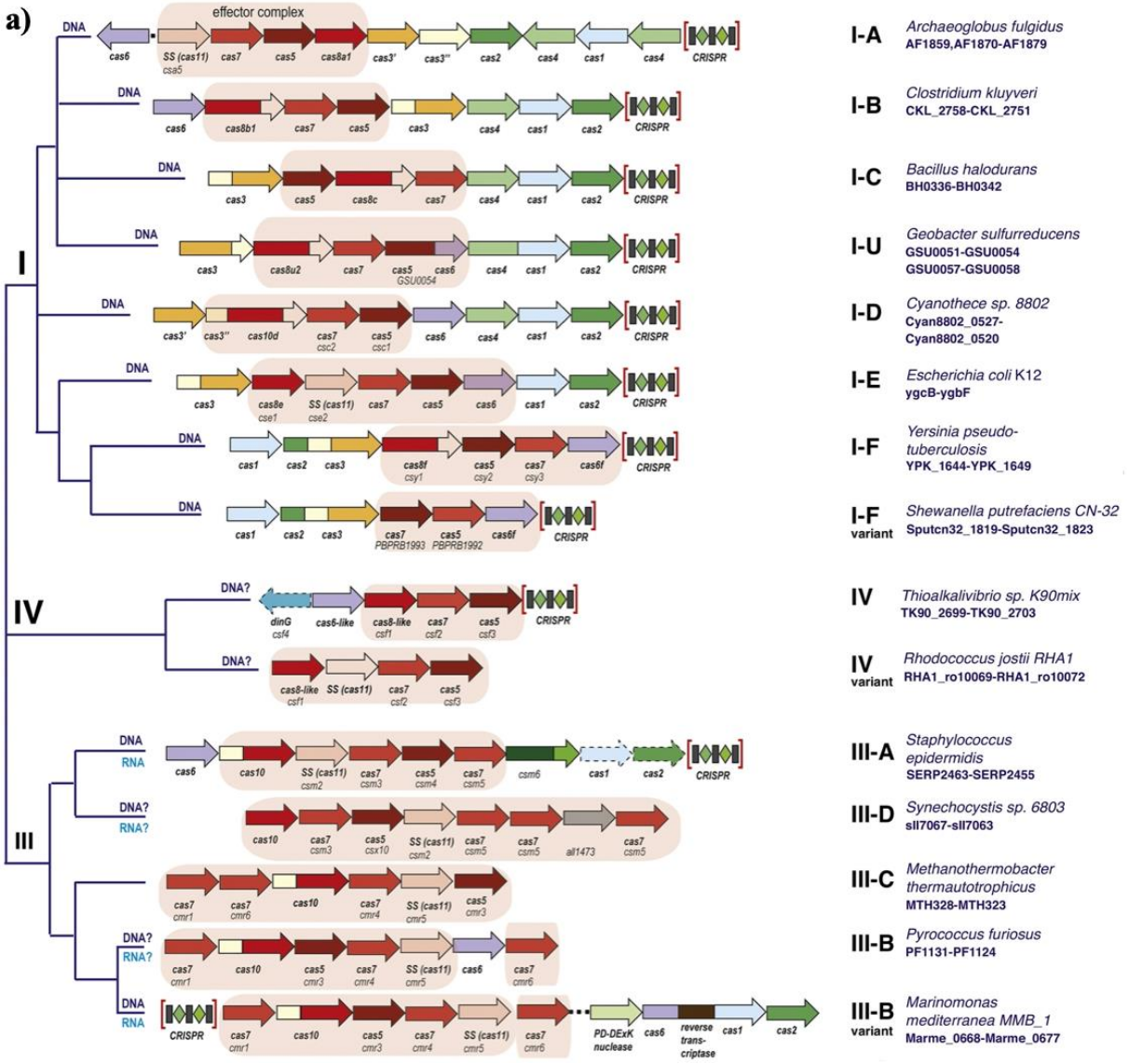

Figure 1: Classification of CRISPR systems. a) class I CRISPR systems. The Cas proteins that make up the multi-subunit effector complexes are highlighted. Target (DNA or RNA) of the nuclease effector is shown. **b)** Class II CRISPR systems**.** Reprinted from *Current opinion in microbiology*, **37**, E. V. Koonin, K. S. Makarova, F. Zhan. Diversity, classification and evolution of CRISPR-Cas systems, 67-78, Copyright (2017), with permission from Elsevier.

approach that takes several factors into account: the signature *cas* gene specific for the individual types and subtypes; organization of the gene in CRISPR loci; sequence similarity between multiple shared Cas proteins; phylogeny of Cas1; and the structure of the CRISPR themselves (Koonin et al., 2017; Makarova et al., 2011; Makarova et al., 2015).

Type II CRISPR/Cas9 systems (**Figure 1b**) are abundant in nature, cleave dsDNA efficiently (unlike type IV systems that cleave RNA), and rely on a single Cas protein for cleavage activity (as opposed to the multi-subunit effector complexes in Class 1 systems) (Vandemoortele et al., 2016). Consequently, CRISPR/Cas9 systems are by far the most used CRISPR systems for gene editing and will therefore be the focus of this thesis.

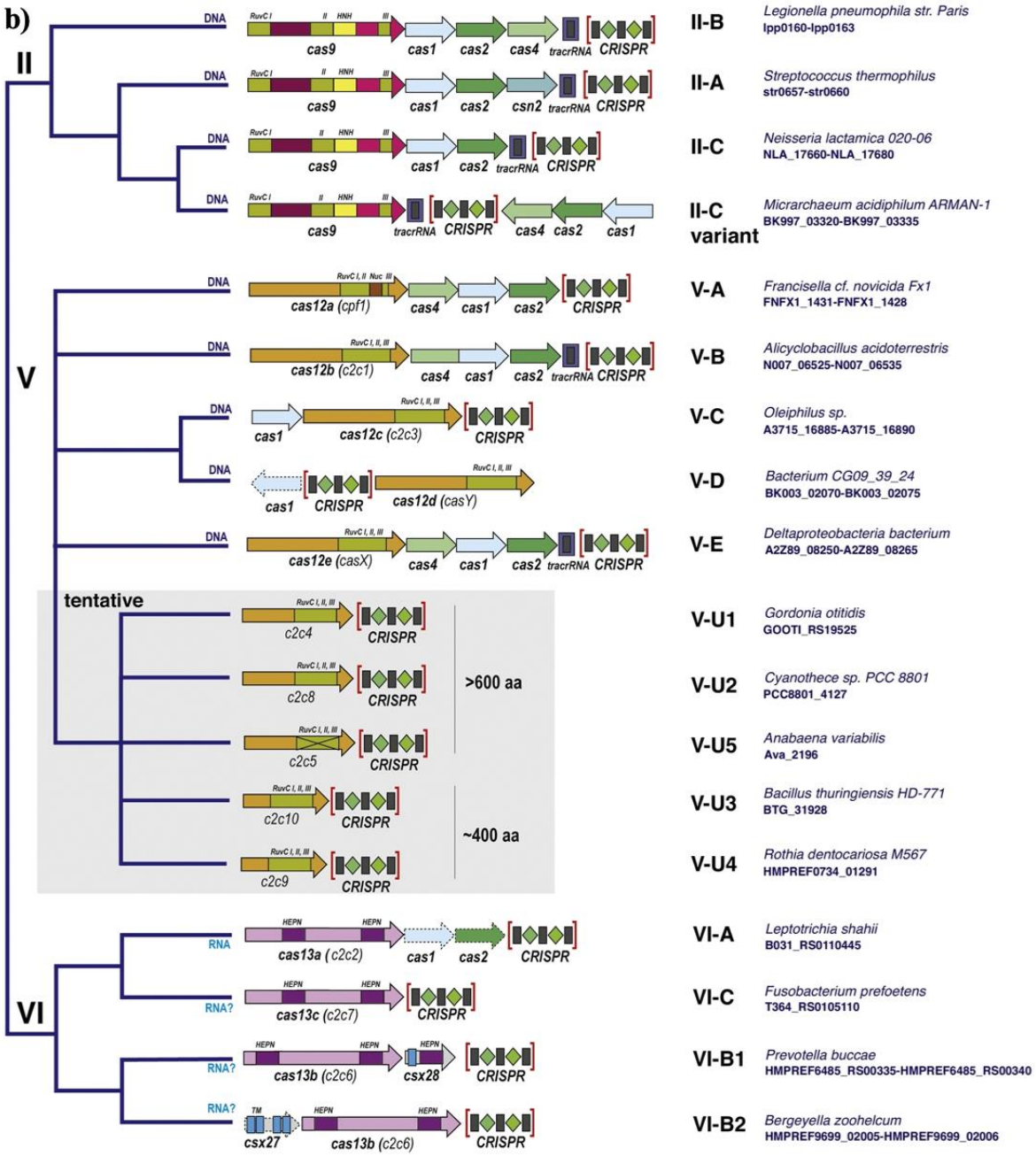

Figure 1: continued

CRISPR/Cas9 STRUCTURE

CRISPR type II locus

CRISPR/Cas adaptive immune systems are encoded by a cluster of genes coding for CRISPR-associated (Cas) proteins (*cas* operon) and a CRISPR array of short repeat sequences interspaced by short segments of non-repeating spacer sequences (**Figure 2**). An AT-rich leader sequence with regulatory elements necessary for acquiring new spacers and promoters for transcription of the CRISPR array is located immediately upstream of the CRISPR array (Alkhnbashi et al., 2016; Brouns et al., 2008; Díez-Villaseñor et al., 2013; Erdmann & Garrett, 2012; Lillestøl et al., 2006; Lillestøl et al., 2009; Yosef et al., 2012). **Cas9** is responsible for target DNA cleavage in all type II CRISPR systems. **Cas1** and **Cas2**, which are responsible for acquiring new spacers, are universal for the vast majority of CRISPR/Cas systems (Error! Reference source not found.).

Antiviral immunity by type II CRISPR/Cas9 systems requires trans-activating CRISPR-RNA (**tracrRNA**), which is a non-coding RNA molecule with partial complementarity to the repeat-sequence (Koonin et al., 2017). A dual RNA hybrid of tracrRNA and crRNA (tracrRNA:crRNA) constitute the guide RNA (**gRNA**) and assembles with Cas9 to form an active surveillance complex. The gene encoding tracrRNA is located within the CRISPR locus but is transcribed separately (Error! Reference source not found.) (Jiang & Doudna, 2017).

The number of repeat-spacer units in the CRISPR array varies greatly between both species and strains. CRISPR array in *Streptococcus pyogenes* contains relatively few repeat-spacer units compared to other streptococcal species such as *S. thermophilus* and *Streptococcus agalactiae*, which can have more than 30 spacers (Le Rhun et al., 2019; Lopez-Sanchez et al., 2012; Nozawa et al., 2011). Other species can have several hundred repeat-spacer units (Karginov & Hannon, 2010). Repeats vary in length and sequence among different species (Kunin et al., 2007) but are identical within a given genome (Karginov & Hannon, 2010).

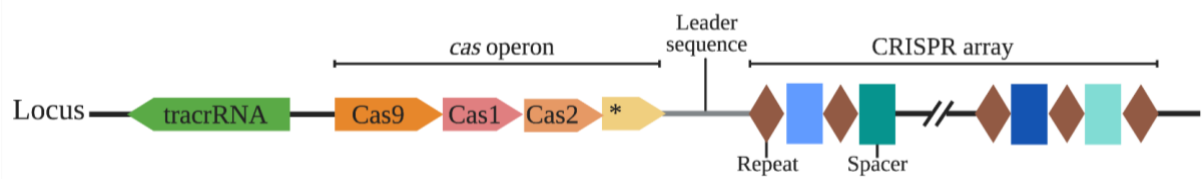

Figure 2: CRISPR locus in type II CRISPR/Cas systems. A typical CRISPR type II locus comprises trans-activating CRISPR-RNA (tracrRNA) gene, genes encoding Cas proteins (cas operon), a leader sequence, and the CRISPR array. The CRISPR array consists of repeating elements (repeats, brown diamonds) interspersed by non-repeating spacer sequences (colored boxes) acquired from previous invading nucleic acids. Cas9, Cas1 and Cas2 are universal for all type II CRISPR systems. The leader sequence located in close proximity to the CRISPR array regulates the integration of new spacers and promotes transcription of the CRISPR array. *Cas4, Csn2, or absent, depending on the subtype (see figure 1b). Created with BioRender.com.

Spacers are highly variable in sequence but are similar in length within a given genome (Karginov & Hannon, 2010). New spacers are integrated upstream of the first repeat (Nuñez et al., 2015), resulting in high spacer-sequence diversity at the leader sequence end of the array. Spacers at the distal end of the cluster are more likely to be shared among strains (Horvath et al., 2008; Lillestøl et al., 2006; Pourcel et al., 2005).

CRISPR-associated nuclease protein 9 (Cas9)

CRISPR-associated protein 9 (**Cas9**) is the multifunctional RNA-guided endonuclease responsible for DNA cleavage in type II CRISPR systems. Recognition and cleavage of target sequence require activation of Cas9 by forming a complex with guide RNA (**gRNA**). In order to avoid cleavage of the spacer sequence within the CRISPR array (auto-immunity), Cas9 cleavage of the target sequence requires the presence of a short protospacer adjacent motif (**PAM**) sequence immediately downstream of the target site. In addition to its central role in DNA cleavage, Cas9 has indispensable roles in the acquisition of new spacers (Heler et al., 2015) and maturation of **pre-crRNA** (Deltcheva et al., 2011).

Cas9 proteins are abundant among bacterial species, and the many different orthologs share the same conserved structural core but differ in size and sequence (Chylinski et al., 2013; Jinek et al., 2014). *S. pyogenes* Cas9 (SpCas9) and *Streptococcus aureus* (SaCas9) are the predominant orthologs in gene editing (Charlesworth et al., 2019; Jiang & Doudna, 2017), mainly due to accessibility and simplicity (Roy et al., 2018). However, the relatively large size of SpCas9 (1368 amino acids) can preclude certain methods for cellular delivery. Using smaller Cas9 proteins, such as SaCas9 (1053 amino acids), can therefore be advantageous. Besides, pre-existing immunity against *S. pyogenes* and *S. aureus* is detected in ~80% of healthy individuals (Kolata et al., 2015; Mortensen et al., 2015) and may complicate gene editing substantially by decreasing the efficiency of gene therapy with SpCas9 or SaCas9 on patients with pre-existing immunity (Mehta & Merkel, 2020). Pre-existing immunity is also suggested to pose a significant risk for inflammatory immune response and toxicity when treated *in vivo* with SpCas9 and SaCsa9 (Charlesworth et al., 2019; Mehta & Merkel, 2020; Wilson, 2009).

S. pyogenes Cas9 (SpCas9) is a large multidomain nuclease enzyme with two distinct lobes, recognition (REC) lobe and nuclease (NUC) lobe (**Figure 3**), connected through an arginine-rich bridge helix and a disordered linking segment (Jiang & Doudna, 2017; Jinek et al., 2014). The NUC lobe contains the two nuclease domains, HNH and RuvC, and a variable C-terminal domain (CTD) containing the PAM-interacting site (Jiang & Doudna, 2017; Jinek et al., 2012). REC lobe consists of three α-helical domains (I – III) and is responsible for

recognizing target DNA (Jiang & Doudna, 2017). The arginine-rich bridge helix is suggested to be involved in guide RNA and/or DNA binding (Jinek et al., 2014; Sampson et al., 2013).

Structural studies show that Cas9 undergoes at least two conformational changes during the defense mechanism. Firstly, RNA-binding causes substantial conformational changes that enable Cas9 to search for PAM sequence. The PAM-recognition region is highly disordered when unbound to guide RNA (apo state), suggesting that Cas9 is inactive and unable to search for target sequence prior to binding to guide RNA (Jiang & Doudna, 2017; Jinek et al., 2014). This is consistent with studies indicating that apo-Cas9 is unable to participate in spacer

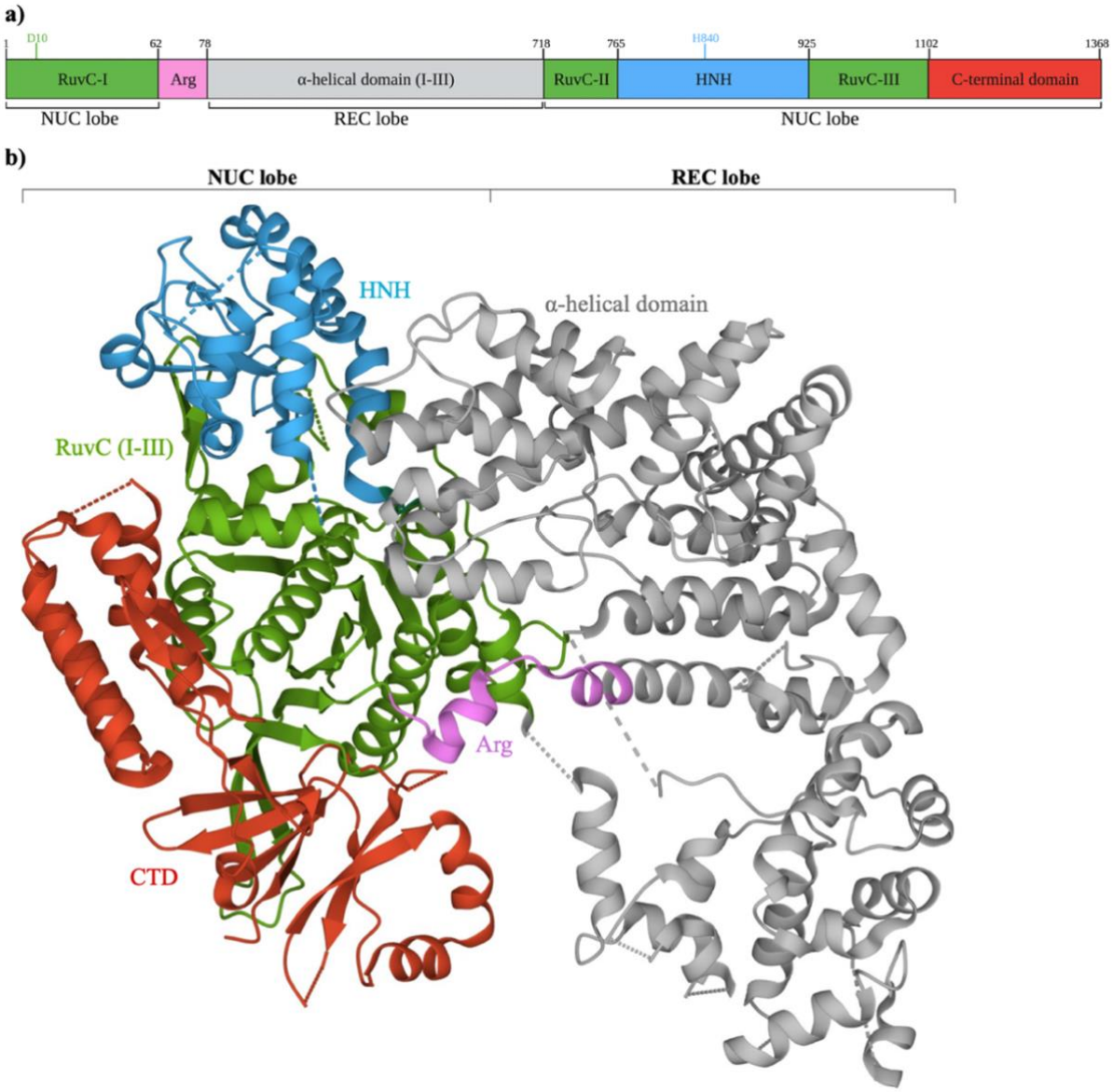

Figure 3: organization and structure of *S. pyogenes* Cas9. a) Schematic representation of regions and domains in *S. pyogenes* Cas9 (SpCas9). D10 and H840 represent key residues for RuvC and HNH cleavage, respectively. Linking segments are not shown. Created with BioRender.com. **b)** Ribbon representation of SpCas9 crystal structure in apo state. Arg, Arginine-rich bridge helix; CTD, C-terminal domain. PDB ID 4CMP (Jinek et al., 2014) created/colored with Mol* (Sehnal et al., 2021) on RCSB PDB (Berman et al., 2000).

acquisition (Heler et al., 2015). The second conformational change occurs upon interaction with the target sequence and moves HNH and RuvC in position for DNA cleavage (Jiang et al., 2016; Palermo et al., 2016; Palermo et al., 2017; Sternberg et al., 2015). This conformational change is suggested to provide additional control to ensure avoidance of **off-target** cleavage (Chen et al., 2017; Dagdas et al., 2017).

Metal-dependent nucleolytic domains called HNH and RuvC are responsible for generating double-stranded DNA cleavage. HNH cleaves the DNA strand complementary to guide RNA (i.e., the target sequence), and RuvC cleaves the non-complementary DNA strand. Highly conserved histidine residue (H840) in HNH and aspartate residue (D10) in RuvC indicates that the nuclease domains uses a one-metal ion catalytic mechanism and a two-metal ion catalytic mechanism, respectively (Nishimasu et al., 2014). This is consistent with studies showing that mutation of one or both of the conserved nucleolytic residues (H840 in HNH and D10 in RuvC) abolishes the catalytic activity in the respective domain (Jinek et al., 2012). Mutation in one of the nucleolytic residues converts Cas9 to a nickase (**nCas9**) which cleaves only one DNA strand. Mutation of both H840 and D10 results in catalytically dead Cas9 (**dCas9**) with no DNA cleavage activity but unchanged DNA binding ability. dCas9 can bind to DNA and reversibly inhibit transcription (Qi et al., 2013).

CRISPR/CAS9 MECHANISM

The CRISPR antiviral defense mechanism occurs in three steps: Acquisition of spacer; expression and maturation; and DNA interference. First, spacer acquisition creates an immunological memory by integrating a part of the invading nucleic acid into the CRISPR array (**Figure 4a**). This immunological memory is transcribed and processed into guiding RNA molecules in the expression and maturation phase (**Figure 4b**). Finally, a nuclease effector protein in complex with guide RNA recognizes and destroys the invader if the bacteria encounter a second attack (**Figure 4c**).

Acquisition of spacer (adaption)

Acquisition of CRISPR-Cas spacer sequences is a multi-step process in which the bacteria incorporate a small specific genetic element from the invading phage or plasmid into the CRISPR array to create an immunological memory (**Figure 4a**) (Amitai & Sorek, 2016; Bolotin et al., 2005; Mojica et al., 2009; Yosef et al., 2012). When the bacteria detect a foreign nucleic acid, it extracts a specific sequence (protospacer) from the invader. The protospacer is then

incorporated as a spacer at the 5´end of the CRISPR array immediately adjacent to the leader sequence and causes the first repeat of the CRISPR array to be extended (Alkhnbashi et al., 2016; Mojica et al., 2009; Pourcel et al., 2005; Yosef et al., 2012). A 5 bp leader-anchoring site at the 3´end of the leader sequence ensures integration at the 5´end of the CRISPR array, possibly to provide a better defense by prioritizing immunity to the most immediate threat (McGinn & Marraffini, 2016; Wright & Doudna, 2016).

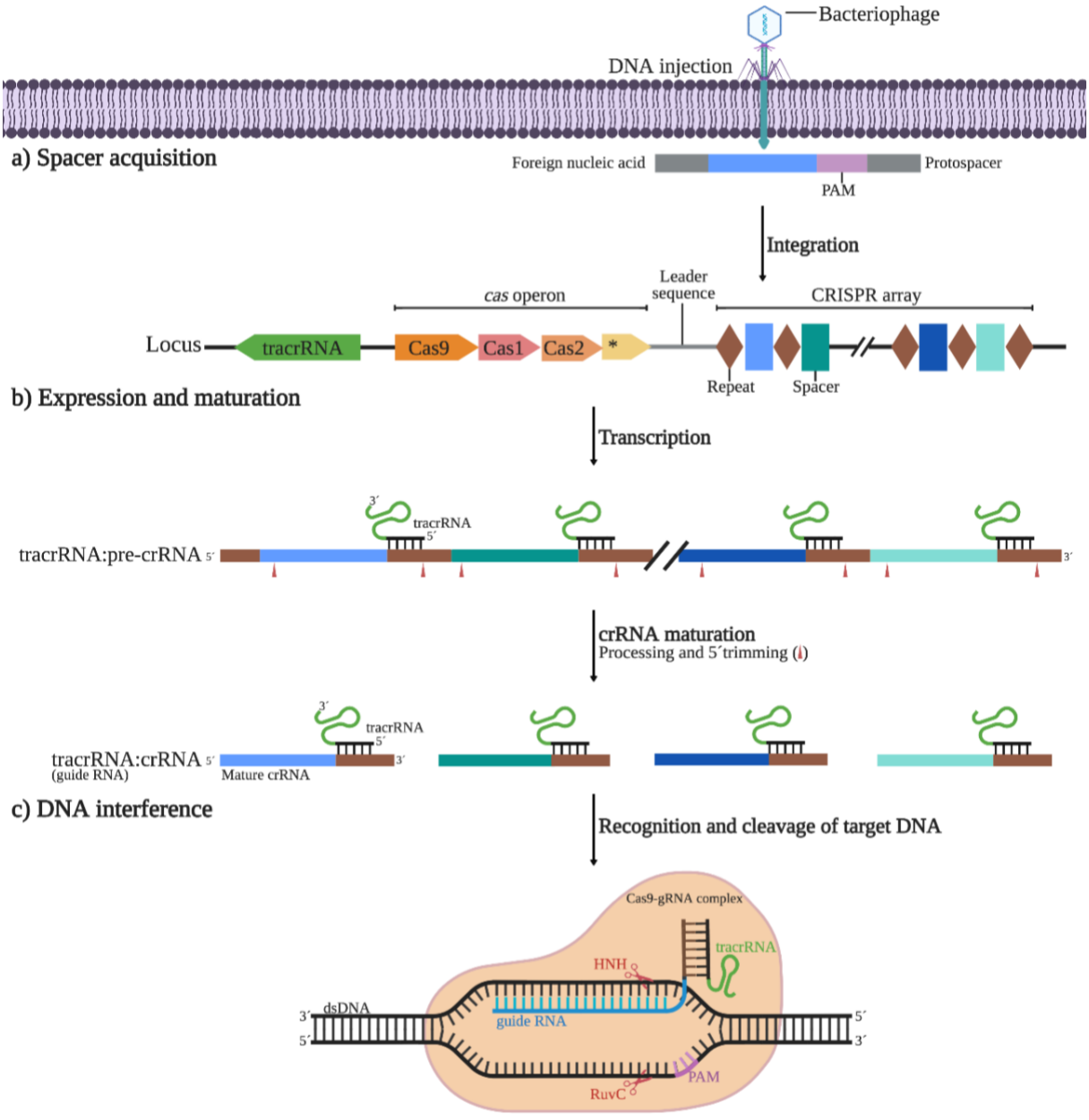

Figure 4: CRISPR-Cas9 mechanism in bacteria. a) Upon detection of foreign nucleic acid, a small part of the invader's genome (spacer, colored boxes) is inserted into the CRISPR array upstream of the first repeat (brown diamonds). **b)** pre-crRNA is transcribed from the CRISPR array and processed into mature crRNA containing a 20 nt guide sequence. **c)** Cas9 in complex with guide RNA (tracrRNA:crRNA) probes DNA for correct PAM and target sequence complementary to crRNA guide sequence. Recognition of target sequence and subsequent double-stranded DNA cleavage by HNH and RuvC removes the invading nucleic acid from the bacterial genome. *Cas4, Csn2, or absent, depending on the subtype. Created with BioRender.com and adapted from Jiang and Doudna (2017)

Despite the high diversity of Cas proteins among CRISPR systems, **Cas1** and **Cas2** nucleases are universally conserved across CRISPR systems (Makarova et al., 2011) and form a stable complex required for the acquisition of new spacers (Amitai & Sorek, 2016; Nuñez et al., 2014; Yosef et al., 2012). Although both Cas1 and Cas2 are endonucleases, mutational studies have shown that only Cas1 endonuclease activity is necessary for spacer acquisition (Nuñez et al., 2014).

In addition to the universal **Cas1-Cas2 adaption module**, spacer acquisition type II CRISPR systems are dependent on Cas9 to select a functional spacer (Heler et al., 2015; Wei et al., 2015). Due to the requirement of PAM during the DNA interference stage, the spacer must have an immediately adjacent PAM sequence. A spacer sequence without an adjacent PAM sequence will not be recognized by Cas9 and thus not provide immunity. Studies of type I-E CRISPR systems in *E. coli* show that Cas1 and Cas2 are sufficient to acquire new spacers, which indicates that Cas1 and Cas2 have some intrinsic PAM recognition ability (Datsenko et al., 2012; Díez-Villaseñor et al., 2013; Yosef et al., 2012). In contrast, studies report that type II CRISPR systems do not acquire new spacers in the absence of either Cas9 or tracrRNA (Heler et al., 2015), suggesting that Cas9 is required for spacer acquisition. The requirement for tracrRNA is consistent with Cas9 being inactive in apo state and that RNA-binding to Cas9 mediates conformational activation (Jinek et al., 2014). Furthermore, mutational studies showed that mutations reducing the PAM binding properties of Cas9 resulted in acquisition of non-functional spacers (i.e., spacers without the proper PAM sequence) (Heler et al., 2015).

Expression and maturation

CRISPR array is transcribed into a long precursor CRISPR RNA (**pre-crRNA**) by a promoter located within the leader sequence upstream of the CRISPR array (**Figure 2**). Pre-crRNA contains all the spacers and repeats, and a two-step maturation process is necessary to generate the mature crRNA containing a 20 nucleotide (nt) guide sequence that directs Cas9 to the target site (**figure 4b**) (Jiang & Doudna, 2017). Transcription of tracrRNA, recruitment of Cas9, and RNase III encoded by genes outside the CRISPR locus are essential for the maturation process (Deltcheva et al., 2011).

Cas9 facilitates base pairing between trans-activating CRISPR RNA (tracrRNA) and the repeat sequence of pre-crRNA and forms a stable tracrRNA:pre-crRNA-Cas9 complex (Le Rhun et al., 2019). This complex is recognized by RNase III, which then carries out the first maturation process by cleaving both tracrRNA and pre-crRNA (Deltcheva et al., 2011). Further maturation of crRNA to 39-42 nt mature crRNA by unknown nucleases results in an active

tracrRNA:crRNA-Cas9 complex ready for DNA interference (**Figure 4c**)(Deltcheva et al., 2011; Le Rhun et al., 2019).

To simplify the system to be used in gene editing, an artificial single guide RNA (sgRNA) that combines tracrRNA and crRNA into a single RNA transcript can be programmed to target virtually any DNA sequence of interest [7] (Jinek et al., 2012).

CRISPR interference

Upon search for target sequence, RNA-bound Cas9 probes the sequence for the correct PAM-sequence (5´-NGG-3´ for SpCas9; 5´-NNGRRT-3´ for SaCas9) and quickly dissociates if PAM is incorrect (Jiang & Doudna, 2017). PAM in close proximity to the crRNA-targeted sequence in the invading nucleic acid is crucial for distinguishing between self and non-self nucleic acid upon the search for target DNA (Deveau et al., 2008; Mojica et al., 2009; Westra et al., 2013). Detection of correct PAM results in melting of the double-stranded DNA, enabling the 20-nt guide sequence to check for complementary with the target sequence upstream of PAM (**Figure 4c**) (Anders et al., 2014; Jiang & Doudna, 2017).

A so-called seed sequence within the 20-nt spacer region in guide RNA is particularly crucial when checking for complementarity between gRNA and target sequence (Semenova et al., 2011; Wiedenheft et al., 2011). The seed sequence in type II CRISPR systems, defined as the 10-12 PAM proximal nucleotides, is located in the 3´end of the guide sequence (Cong et al., 2013; Jiang et al., 2013; Jinek et al., 2012; Sternberg et al., 2014). Mismatches within the seed region halt DNA cleavage, whereas mismatches outside this region are generally more accepted (Cong et al., 2013; Jinek et al., 2012; Pattanayak et al., 2013). Sufficient complementarity leads to the formation of a PAM-proximal R-loop structure by displacing the non-complementary strand while the guide sequence remains bound to the complementary strand (Jinek et al., 2012; Szczelkun et al., 2014).

Conformational changes of Cas9 upon binding to target sequence and formation of R-loop displaces the HNH domain to the proper position for cleavage of the complementary strand (Jiang et al., 2016). Allosteric communication between HNH and RuvC through two hinge regions ensures simultaneous activation of RuvC catalytic activity by placing the non-complementary strand in the RuvC active site (Jiang et al., 2016; Sternberg et al., 2015). Cleavage of the double-stranded target DNA results in blunt-ended dsDNA break (DSB) 3 bp upstream of PAM (**Figure 4c**) (Garneau et al., 2010; Gasiunas et al., 2012).

[7] Further explanation in Chapter 3: Germline editing with CRISPR/Cas9

CHAPTER 3

GERMLINE EDITING WITH CRISPR/CAS9

An important question in the **germline editing** debate is whether the risks associated with germline editing are worse than the consequence of not correcting the disease. Despite the many attempts to enhance specificity and efficiency, challenges with potential **off-target** mutations and high prevalence of **mosaicism** in gene-edited embryos remain unresolved, despite the many attempts to enhance specificity and efficiency. The fact that edits in the germline have the potential to affect subsequent generations raises additional concerns regarding safety. Some have expressed worries about the possibility of unpredictable risks and thus called for a moratorium on human germline editing:

> In our view, genome editing in human embryos using current technologies could have unpredictable effects on future generations. This makes it dangerous and ethically unacceptable. Such research could be exploited for non-therapeutic modifications (Lanphier et al., 2015).

This argumentation has been met with some criticism saying this is not sufficient to justify a ban. Savulescu et al., stated that "nearly all new technologies have unpredictable effects on future generations…and though they could be catastrophic (for example, through cyberterrorism), this does not mean on balance they should be banned. Their expected benefits outweigh their expected harms" and that "the mere fact that a technology could be used non-therapeutically doesn't warrant a moratorium on its use" (Savulescu et al., 2015). Nonetheless, there is a general agreement on the necessity of further improvements and validations of the technology before implementing CRISPR/Cas9 for clinical applications (Baltimore et al., 2015; Lander et al., 2019; Lanphier et al., 2015). The Second International Summit on Human Gene Editing, which was held in November 2018, concluded that:

> The scientific understanding and technical requirements for clinical practice remain too uncertain and the risks too great to permit clinical trials of germline editing at

> this time. Progress over the last three years and the discussions at the current summit, however, suggest that it is time to define a rigorous, responsible translational pathway toward such trials. (National Academies of Sciences, Engineering, and Medicine, 2019 p. 7)

One of the fundamental principles in biomedical ethics is that the expected benefit should always outweigh the risk. 'Risk' refers to the possibility of future harm and can be evaluated in terms of probability and magnitude of possible harm (Beauchamp & Childress, 2001). 'Benefit' refers to the positive values (e.g., improved health and saved lives) that are gained and are best compared to harm rather than the risks of harm. The risks relative to the benefits can be assessed by a risk-benefit analysis (RBA), usually in terms of a ratio between the probability and magnitude of expected benefit and the probability and magnitude of risks (Beauchamp & Childress, 2001).

The benefits and some risks differ significantly according to the specific gene target. Hence, every possible application of CRISPR/Cas germline editing must be evaluated independently in the establishment of regulations and guidelines. This is the basis of the 'translational pathway' to human germline editing proposed by Julian Savulescu and Peter Singer. An ethically justifiably pathway should, according to them, start with catastrophic single-gene disorders, followed by severe single-gene disorders, then reduction in the genetic contribution to common diseases, and enhanced immunity and perhaps even delaying aging at last (Savulescu & Singer, 2019).

One problem with balancing risks and benefits in the case of germline editing is that the perception of risk and the value of a consequence is strongly subjective. Since germline editing must be done at the embryonic stage, the (future, some would say) person that will have to live with the consequences have no say in whether the genetic intervention should take place or not. However, bearing in mind the severity of some monogenic diseases that can be cured with CRISPR, it is hard to see how any negative effect can be worse than the disease itself. Consider the consequence of increased risk of cancer due to off-target mutations knocking out a tumor suppressor gene. How severe does the disease have to be before the increased risk of cancer no longer outweighs the benefits? Does the risk outweigh the benefits of germline editing in the following three cases?

CASE 1: TAY SACHS DISEASE

Tay Sachs disease is a progressive neurodegenerative disease caused by a mutation in the HEXA (hexosaminidase A) gene encoding the α-subunit of the enzyme β-hexosaminidase (Gravel et al., 1991). Symptoms usually start 3–6 months after birth and include developmental retardation, seizures, blindness, deafness, paralysis, dementia, etc. There is no cure for Tay Sachs, and the disease is usually fatal by the age of three to five.

CASE 2: HUNTINGTON'S DISEASE

Huntington's disease is a progressive neurodegenerative disease caused by an elongated CAG repeat (36 or more repeats) in the *HTT* gene encoding the huntingtin protein (Georgiou-Karistianis et al., 2008; Roos, 2010). The onset of symptoms is usually around age 30–50 but varies depending on the number of CAG repeats; the longer the repeats are, the earlier the onset will be. More than 50 repeats usually cause juvenile onset (before the age of 20). Symptoms include chorea and dystonia (involuntary movement), cognitive impairments (changes in personality and problems with concentration, memory, impulse control, etc.), depression, anxiety, etc. The symptoms gradually worsen and result in death, usually 15-20 years after the first symptom.

CASE 3: HIV RESISTANCE (CCR5Δ32)

Human immunodeficiency virus (HIV) is a major global public health issue. World Health Organization reported 680 000 deaths caused by HIV in 2020 (World Health Organization, 2021). HIV infection can be asymptomatic in the first few months, but some will get influenza-like symptoms. The symptoms, will after a while, include swollen lymph nodes, fever, cough, diarrhea, and weight loss. The immune system weakens, and the infected individual will thus become more susceptible to infections such as pneumonia and tuberculosis, as well as some types of cancers. HIV has no cure but can be managed by a combination of antiretroviral (ARV) drugs.

APPLICATIONS

The prokaryotic CRISPR/Cas9 immune system confers a simple two-component (Cas9 nuclease and guide RNA) programmable system for site-specific gene editing in virtually any type of cell (Cong et al., 2013; Jinek et al., 2012; Jinek et al., 2013; Mali et al., 2013). Engineering a single guide RNA (**sgRNA**) chimera that mimics the bacterial dual-RNA guide (tracrRNA:crRNA) enables easy programming of CRISPR/Cas9 to target any sequence of interest, provided that the proper **PAM** sequence is present immediately adjacent to the target sequence (Jinek et al., 2012). As in the bacterial CRISPR/Cas immune system, detection of correct PAM and subsequent base pairing between guide sequence and target sequence trigger Cas9 to induce sequence-specific cleavage of target sequence three bp upstream of PAM (Jinek et al., 2012). The double-stranded DNA break (DSB) is repaired via non-homologous end joining (**NHEJ**) or homologous direct repair (**HDR**) (**Figure 5**) (Takata et al., 1998) by the cells' DNA repair mechanism. NHEJ is active throughout the entire cell cycle and is the predominant DNA repair mechanism in mammalian cells, often resulting in random indels and substitutions at the break site (Lieber, 2010; Mao et al., 2008). In contrast, HDR uses a donor DNA template to introduce a specific mutation at the DSB site but is active only during cell cycle phases S and G2 (Shrivastav et al., 2008).

Several approaches have been developed for introduction of various mutations, including knock-out (loss-of-function), knock-in (gain-of-function), gene correction (restoration of function), and regulation of gene expression (reversible inhibition of transcription). Knock-out approaches are the simplest form of gene editing and are especially useful for creating disease models and **genotype-phenotype correlations** studies. Knock-out is achieved by introducing random indels within the gene or by introducing a premature stop codon (Kuscu et al., 2017). A significant advantage with gene knock-out approaches is that it is not contingent on homologous direct repair (HDR). In contrast, knock-in and gene correction approaches are generally contingent on HDR (Roy et al., 2018). DSBs are preferentially repaired through NHEJ, and despite the development and improvement of several methods to increase HDR frequency, efficient knock-in remains challenging (Auer et al., 2014; Irion et al., 2014; Shi et al., 2015).

Regulation of gene expression is achievable by using catalytically inactivated Cas9. Mutations of the active nuclease residues D10 and H840 inactivate cleavage activity without altering DNA binging activity, thereby enabling Cas9 to inhibit transcription of specific genes (Gilbert et al., 2013; Hilton et al., 2015; Kearns et al., 2015; Qi et al., 2013). st (Yin et al., 2014),

germ cells (Long et al., 2014; Wu et al., 2015), stem cells (Schwank et al., 2013), and induced pluripotent stem cells (iPSCs) (Li, H. L. et al., 2015; Li et al., 2016; Park et al., 2015; Smith et al., 2015; Song et al., 2015; Xie et al., 2014; Xu et al., 2015).

Extensive research on somatic- and germline editing in a wide variety of species has been conducted over the past decade. The first report on CRISPR/Cas9-mediated human germline editing was published in 2015 (Liang et al., 2015). Despite using non-viable (tripronuclear) zygotes, the experiment sparked a debate on whether to proceed with or prohibit research on human germline editing (Baltimore et al., 2015; Lanphier et al., 2015). However, the world's first experiment on human germline editing using viable embryos was approved in the UK at

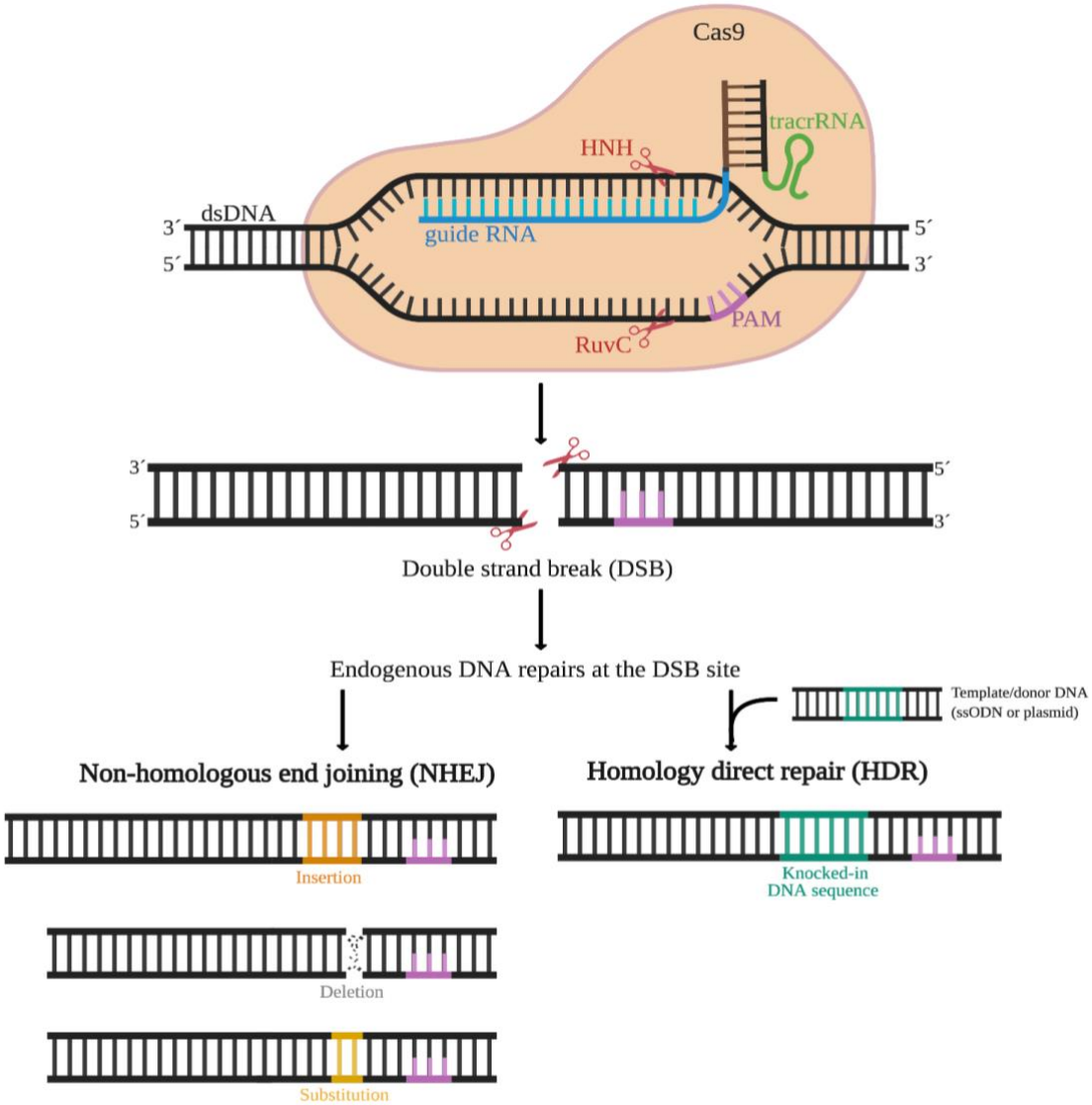

Figure 5: Repair of double-strand DNA breaks (DSBs) created by Cas9. Upon DNA cleavage, the DSB is repaired by the cell's DNA repair machinery. The cell will use error-prone non-homologous end joining (NHEJ) to repair the DSB in the absence of DNA template, which will lead to random indels or substitutions. Homology direct repair creates specific modifications but is contingent on the cell cycle as well as the presence of donor template DNA. Created with BioRender.com.

the beginning of 2016 (The Francis Crick Institute, 2016). Several experiments on heritable germline editing using human embryos have been conducted since then, although most research is conducted using non-human embryos (**Table 1**) due to strict regulation and/or prohibition of heritable gene editing in most countries (Baylis et al., 2020).

The development of CRISPR/Cas technology has already revolutionized scientific research and medicine in several ways by simplifying a range of experimental pipelines. The simple and versatile tool for site-specific gene editing holds immense opportunities in medicine, including treatment and prevention of devastating genetic diseases. Close to 6000 disease phenotypes are so far found to be caused by mutations in one single gene (Online Mendelian Inheritance in Man, OMIM®), and the current treatment alternatives for most of these diseases are either inefficient or non-existent. With the scarce treatment options and an estimated prevalence of 5–7% of the population (National Academy of Sciences, 2017; Verma & Puri, 2015), genetic diseases put a significant burden on human health. CRISPR/Cas technology confers a revolutionizing potential to cure – or rather prevent – genetic diseases by correcting disease-causing mutations in the genome of gametes or early-stage embryos.

CRISPR has shown encouraging results as a potential cure for monogenic diseases such as cataracts (Wu et al., 2013; Wu et al., 2015), Duchenne muscular dystrophy (Long et al., 2014), hypertrophic cardiomyopathy (Ma et al., 2017), β-Thalassemia (Liang et al., 2017). Existing and well-established reproduction technologies such as preimplantation genetic testing (PGT) can be used to avoid heritable disease in offspring by performing genetic testing of the embryos prior to implantation. However, PGT is limited to the genetic characteristics of the parents and will, in some cases, be ineffectual due to the lack of unaffected embryos. The only available option to conceive a child free from the disease then is to keep trying, but the high price tag of PGT and the emotional and physical impact of repetitious failed attempts put the prospective parents in a hopeless situation. These situations are rare[8] but can nonetheless be devastating for those in them. Implementation of CRISPR/Cas germline editing in assisted reproductive technology can give people in such situations a less invasive alternative to conceive a healthy child, as well as save the future child from a devastating disease.

[8] A study from 2009 showed that 7.1% of PGT cycles result in no unaffected embryos available for transfer (Gutiérrez-Mateo et al., 2009)

Table 1: Examples of CRISPR/Cas9-mediated germline editing experiments

Approach	Gene	Delivery method	Ref.
HUMAN GERMLINE EDITING			
Gene correction	*MYBPC3* (Hypertrophic cardiomyopathy)	Microinjection of Cas9 protein, sgRNA and ssODNs into the embryo.	(Ma et al., 2017)
		Co-injection of Cas9 protein, sgRNA, ssODNs and sperm into the egg.	
	HBB (*β*-globin)	Microinjection of Cas9 mRNA, gRNA, GFP mRNA and ssDNA oligo into 3NP zygote.	(Liang et al., 2015)
		Microinjection of Cas9 protein, sgRNA and ssODNs into 2PN zygote.	(Tang et al., 2017)
	G6PD (glucose-6-phosphate dehydrogenase)	Microinjection of Cas9 protein, sgRNA and ssODNs into 2PN zygote.	(Tang et al., 2017)
	EYS	Microinjection of RNPs into two-cell stage embryo.	(Zuccaro et al., 2020)
Knock-out	*CCR5*	Microinjection of Cas9 mRNA and gRNA into tripronuclear (3NP) embryo.	(Kang et al., 2016)
	POU5F1	Microinjection of RNPs into zygote	(Fogarty et al., 2017)
NON-HUMAN GERMLINE EDITING			
Gene correction	*Crygc* (cateracts)	Microinjection of Cas9 mRNA, sgRNA and ssODNs into mouse zygotes	(Wu et al., 2013)
	Dmd (dystrophin, Duchenne Muscular Dystrophy)	Microinjection of Cas9 mRNA, sgRNA and ssODNs	(Long et al., 2014)
Knock-out	*CCR5*	Microinjection into Mauritian cynomolgus macaque embryos	(Schmidt et al., 2020)
	Nr0b1 (Nuclear Receptor), *Ppar-γ* (Peroxisome Proliferator-Activated Receptor) and *Rag1* (Recombination Activator)	Microinjection of Cas9 mRNA and five different sgRNA (two sgRNA targeting *Nr0b1*, two sgRNA targeting *Ppar-γ* and one sgRNA targeting *Rag1*) into one-cell cynomolgus monkey zygote.	(Niu et al., 2014)
	ASPM (abnormal spindle-like microcephaly-associated protein)	Microinjection of Cas9 protein and gRNA into monkey zygote	(Tu et al., 2017)
		Microinjection of Cas9 mRNA and gRNA into monkey zygote	

CRISPR/Cas also provides a potential therapeutic strategy for genetic diseases caused by additional chromosomes (trisomy) by targeted chromosome deletion (Adikusuma et al., 2017; Zuo et al., 2017). Aneuploidy, i.e., the presence of an abnormal chromosome number in a cell, is a common cause of genetic diseases and is strongly associated with cancer. Around 1 of 160 live-born children have chromosomal abnormalities, of which Down's syndrome (trisomy 21), Edward's syndrome (trisomy 18), and Patau syndrome (trisomy 13) account for the majority of cases (Driscoll & Gross, 2009). Both trisomy 18 and 13 are associated with high lethality – under 10 % of affected children survive for longer than a year (Driscoll & Gross, 2009).

Targeted deletion of specific chromosomes is based on the hypothesis that generating multiple DSBs at targeted chromosomal locations can induce chromosomal deletion (Zuo et al., 2017). A study by Adikusuma et al. (2017) showed that CRISPR/Cas-mediated fragmentation of the centromere led to an efficient loss of the Y chromosome. An alternative approach based on fragmentation of the long chromosomal arm instead of the centromere also led to targeted chromosome deletion (Adikusuma et al., 2017). The latter strategy can be applied in both dividing and non-dividing cells because it does not target the centromere.

In addition to its groundbreaking potential to cure horrible genetic diseases, CRISPR technology offers a range of practical approaches in medical research, including genome imaging (Anton et al., 2014; Chen et al., 2013; Deng et al., 2015; Ma et al., 2015; Tanenbaum et al., 2014), molecular diagnosis of infectious diseases (Abudayyeh & Gootenberg, 2021; Chen et al., 2018; Myhrvold et al., 2018), epigenetic modification, and regulation of gene expression (Gilbert et al., 2013; Hilton et al., 2015; Kearns et al., 2015; Qi et al., 2013). The efficient and versatile tool for targeting specific genes allows elucidation of gene function and genotype-phenotype correlations. Cas9 can be programmed to target multiple genes simultaneously, thereby enabling researchers to examine several genes in one experiment (Cong et al., 2013). This is especially useful when studying complex polygenic traits and diseases. Generating animal models of human diseases can give a deep insight into pathogenesis and are useful in the development and improvement of treatment approaches (Chen et al., 2015; Ma et al., 2014a; Ma et al., 2014b; Mizuno et al., 2014; Tschaharganeh et al., 2016; Yang et al., 2017).

RISKS AND TECHNOLOGICAL CHALLENGES

Apart from the technological challenges and risks discussed in this chapter, additional consequences may still be undiscovered. Some of these consequences may not be discovered until potential clinical trials, as research on human embryos is either prohibited or strictly regulated in most countries. Most countries that allow research on human embryos demand destruction of the genome-edited embryo within a short period of time after fertilization (14 days in Norway) (Bioteknologiloven, 2003, § 3-2). Consequentially, potential adverse effects (e.g., on embryonic development) arising later than 14 days will not be discovered. Although much can be studied using non-human primates or other research animals, there may be considerable differences between humans and the research species that will lead to failure to detect certain risks.

Cellular delivery of CRISPR components

CRISPR/Cas gene editing is contingent on safe and efficient cellular delivery of the two critical components – Cas9 and guide RNA (gRNA) (Li, L. et al., 2015). In addition, delivery of a donor DNA template with the desired gene mutation is necessary for gene correction and knock-in. Although several delivery methods have been developed, safe and efficient delivery of the CRISPR/Cas system for therapeutic use remains challenging. Both the dose of the donor template and the duration and magnitude of nuclease expression are critical factors for safety and efficiency (Maeder & Gersbach, 2016).

Intracellular delivery of CRISPR/Cas9 for therapeutic application can be achieved by introducing a plasmid or vector encoding Cas9 and the designed sgRNA or by direct delivery of mRNA or preassembled Cas9-sgRNA ribonucleoproteins (RNPs) (Li, L. et al., 2015). Initial experiments relied mainly on vector/plasmid-based delivery. However, these methods are often inappropriate for therapeutic use due to possible risks of cytotoxicity, random insertion of plasmid fragments, presence of bacterial DNA sequences in plasmid backbones as well as low efficiency (Maeder & Gersbach, 2016). Direct delivery of preassembled RNPs has thus become the predominant delivery method for therapeutic gene editing due to generally higher gene editing efficiency and decreased off-target activity than vector-based delivery methods (Kim & Kim, 2014; Wang et al., 2016).

Delivery of RNPs can be achieved through physical approaches (such as electroporation and microinjection) or synthetic carriers (e.g., nanoparticles) (Zhang et al., 2021). Microinjection of RNPs into living cells through a glass micropipette has been used to

successfully deliver the CRISPR/Cas system to embryos, including human embryos (**Table 1**) (Cho et al., 2013; Kim, K. et al., 2017; Ma et al., 2017; Sung et al., 2014; Wu et al., 2013). Although especially useful for embryo gene editing with high specificity, microinjection is technically challenging, expensive, and time-consuming (Kaneko & Nakagawa, 2020; Zhang et al., 2021). As an alternative, delivery of RNPs via electroporation enables efficient delivery to multiple embryos simultaneously. Delivery of RNPs via electroporation is proven to be efficient in mouse, pig, and bovine embryos (Chen et al., 2016; Hashimoto et al., 2016; Miao et al., 2019; Modzelewski et al., 2018; Tanihara et al., 2018; Teixeira et al., 2018; Tröder et al., 2018). However, zygotes of different species show varying sensitivity to electroporation conditions (Miao et al., 2019). More research is necessary to assess electroporation efficiency and safety in human embryos.

Specificity and efficiency

Clinical applications of CRISPR/Cas9 for human germline editing are highly contingent on high specificity and efficiency, and despite the many attempts to improve the technology, this remains a challenge. CRISPR/Cas9 are generally considered to be highly sequence-specific, but the possibility of off-target cleavage activity by Cas9 raises a considerable safety concern for CRISPR gene editing. These mutations pose a significant risk of disrupting normal gene expression and inactivation of otherwise functional genes (Cho et al., 2014; Choi & Meyerson, 2014). For instance, off-target can inactivate genes essential for normal cell function, activate (proto-)oncogenes, or inactivate tumor suppressor genes (e.g., p53, which is central in regulation and control of the cell cycle).

Off-target mutations are predominantly caused by sequence similarity between the target and the off-target sites (sgRNA-dependent off-target). It is, therefore, possible to predict potential off-target sites by searching for sequences that are homologous to the target site sequence. The number of mismatches between sgRNA and target sequence that can be tolerated is dependent on the position and distribution of the mismatches (Cong et al., 2013; Fu et al., 2013; Hsu et al., 2013; Li et al., 2019). Off-target at random sites with no sequence similarity between off-target site and target site has been reported (Schaefer et al., 2017). However, questions are raised on whether these mutations are Cas9-induced, as these mutations may be preexisting or naturally occurring mutations (Kim, S.-T. et al., 2017; Lareau et al., 2018; Lescarbeau et al., 2018; Wilson et al., 2018).

Prediction and detection of off-target effects

Strategies for predicting and detecting off-target mutations can generally be divided into two classes: biased and unbiased. Biased detection of off-target mutations is based on targeted sequencing of potential off-target sites. Since most off-target mutations result from sequence similarity with the on-target site (sgRNA-dependent off-target mutations), potential off-target sites can be predicted based on the sgRNA sequence (Li et al., 2019). Numerous online tools are developed for biased prediction of potential off-target sites (Couvin et al., 2018; Doench et al., 2016; Hsu et al., 2013; Li et al., 2019). The predicted off-target sites can be used for simple, rapid, and cost-efficient detection of off-target mutations by T7 endonuclease I (T7EI) assay, Sanger sequencing, or high-throughput sequencing (Li et al., 2019).

However, if off-target mutations can occur at "random" places in the genome, biased detection of off-target mutations may fail to detect certain incidences. Unbiased detection of off-target activities is based on a genome-wide search for off-target cleavage (Li et al., 2019; Tsai & Joung, 2016). Whole-genome sequencing can be used, but this is generally insensitive and is likely to only detect the off-target mutations with the highest frequency in a cell population (Tsai & Joung, 2014; Tsai & Joung, 2016). Alternatively, GUIDE-seq provides a highly sensitive method for unbiased detection of off-target mutations, but this method requires efficient intracellular delivery of a double-stranded oligodeoxynucleotide (dsODN) tag and is therefore challenging to use *in vivo* (Tsai et al., 2015). Another unbiased method is based on high-throughput genome-wide translocation sequencing (HTGWS), where translocation between a nuclease-induced 'bait' DSB and off-target 'prey' site is detected (Frock et al., 2015). HTGWT is more applicable *in vivo* because it does not require the delivery of any additional components (Tsai & Joung, 2016).

Improving specificity and efficiency

Numerous approaches to increase specificity and efficiency of CRISPR/Cas9 have been developed, involving engineering Cas9, optimizing sgRNA, pairing nCas9, and optimizing the concentration and duration of Cas9-sgRNA. However, improved specificity is often at the cost of high efficiency and vice versa. For instance, different Cas9 orthologs have different PAM requirements, and although longer and more complex PAM decreases off-target mutations, it also reduces efficiency (Li et al., 2019).

Several engineered Cas9 variants have been designed to have enhanced specificity and efficiency (**Table 2**). Designing Cas9 with altered PAM requirements allows for selection of target sites that do not contain the "wild-type" PAM, thereby broadening the targeting range

and allowing selection of potentially more specific target sites (Kleinstiver et al., 2015). Double-nicking of dsDNA by a paired Cas9 nickase (**nCas9**) to generate the double-stranded DNA break is shown to reduce off-target mutations by 50- to 1,500-fold in mouse zygotes (Ran et al., 2013; Shen et al., 2014).

Table 2: Engineered Cas9 variants with improved efficiency and specificity.

Nuclease variant	Purpose	PAM	Reference
HeFSpCas9	Improved specificity	NGG	(Kulcsár et al., 2017)
EvoSpCa9	Improved specificity	NGG	(Casini et al., 2018)
HypaCas9	Improved specificity	NGG	(Chen et al., 2017)
Sniper-Cas9	Improved specificity	NGG	(Lee et al., 2018)
SpCas9-HF1	Improved specificity by reducing non-specific DNA contact without affecting efficiency	NGG	(Kleinstiver et al., 2016)
eSpCas9	Improved specificity by weakening non-target DNA binding and encouraging rehybridization to target DNA strand	NGG	(Slaymaker et al., 2016)
xCas9	Improved specificity and targeting range	NG, GAA, GAT	(Hu et al., 2018)
VQR-SpCas9	Improved targeting range	NGA	(Kleinstiver et al., 2015)
EQR-SpCas9	Improved targeting range	NGAG	(Kleinstiver et al., 2015)
VRER-SpCas9	Improved targeting range	NGCG	(Kleinstiver et al., 2015)
SpCas9-NG	Improved targeting range	NG	(Nishimasu et al., 2018)
SaKKHCas9	Extend PAM and reduce size	NNNRRT	(Kleinstiver et al., 2015)

Obtaining a sgRNA with high specificity is essential for targeting efficiency and prevention of potential off-target effects. This is generally achieved by selecting a target site with the fewest potential off-target sites, meaning that the target sequence should be as unique as possible (Gratz et al., 2015; Wiles et al., 2015). The 10-12 nt seed sequence immediately adjacent to PAM is suggested to be of particular importance regarding specificity. Extra attention should thus be paid to ensure that at least this sequence is unique in the genome (Cong et al., 2013; Jiang et al., 2013; Jinek et al., 2012; Pattanayak et al., 2013; Semenova et al., 2011; Sternberg et al., 2014; Wiedenheft et al., 2011). Mismatches within the seed sequence will

abolish cleavage, but sequences with complementarity with the seed sequence constitute potential off-target sites. Numerous database libraries and online tools have been developed to simplify and optimize the sgRNA design process (Brazelton et al., 2015; Doench et al., 2016; He et al., 2021).

Some approaches to enhance specificity are based on modifying the length of sgRNA. Using a truncated sgRNA shortened by 2-3 nt at the 5´end can reduce the frequency of off-target mutations, possibly by reducing excess binding energy to a level where the CRISPR/Cas system is more sensitive to mismatches (Fu et al., 2014a; Fu et al., 2014b). The hypothesis that truncated sgRNA increases sensitivity to mismatches is consistent with GUIDE-seq analysis showing that most off-target mutations only have one of two mismatches (Fu et al., 2014b; Tsai & Joung, 2016). Other modifications of sgRNA suggested to enhance specificity involve chemical modifications at specific positions in the guide sequence (Cromwell et al., 2018; Ryan et al., 2018) and partial replacement of RNA nucleotides with DNA nucleotides (Yin et al., 2018).

Mosaicism

Genetic **mosaicism** refers to the presence of two or more different **genotypes** within one organism. This phenomenon can occur through several mechanisms (Taylor et al., 2014) and is a common result of germline editing, primarily due to persistent Cas9-mediated gene editing at different stages of embryonic development (Mehravar et al., 2019). Although mosaicism can be useful in genetic research (Chen et al., 2015; Helderman-van den Enden et al., 2009; Markossian & Flamant, 2016; Yasue et al., 2017; Zhong et al., 2015), it is generally an undesirable outcome in germline editing.

Mosaicism in gene-edited embryos is especially problematic because it is impossible to use PGT to ensure correct editing prior to implantation. Testing the genotype in one cell will not be sufficient because it may differ from the genotype in other cells but testing the genotype of multiple cells is not an option because that will destroy the embryo (National Academy of Sciences, 2017). Resultingly, the implanted embryo may have undetected off-target mutations. Also, germline editing resulting in mosaicism will not necessarily benefit succeeding generations, depending on whether the germ cells contain the edited or the “original” genotype (Oliver et al., 2015).

Germline editing resulting in mosaicism will, in many cases, be ineffectual due to only a subset of the cells contains the edited gene while the rest still have the “original” gene. Mosaicism is especially problematic if the target gene codes for essential cell functions or if

the intended mutation is to create resistance to infectious diseases. Mosaic individuals with corrected a disease-causing mutation in only a subset of cells are likely to still suffer from the disease because the disease-causing mutation is present in some of the cells. Likewise, individuals with *CCR5/CCR5Δ32* mosaicism will not be resistant to HIV-1 infection because the virus will still be able to enter and infect the red blood cells without the Δ32 deletion. However, if the corrected gene encodes a secreted factor (e.g., growth hormone or dystrophin), mosaicism can be sufficient to decrease the severity and progression of a disease (National Academy of Sciences, 2017). A study on Duchenne muscular dystrophy (DMD)[9] mosaic mouse showed that correction of the dystrophin (*Dmd*) gene in only a subset of cells was sufficient to gain complete phenotypic rescue (Long et al., 2014).

The mechanisms of mosaicism in germline editing are not fully understood, but factors such as the timing of gene editing relative to the cell cycle phase, the duration of Cas9 activity, and the concentration of injected CRISPR components are suggested to be central in the occurrence of mosaicism (Ma et al., 2017; Mehravar et al., 2019; Wang et al., 2013). Low concentrations of injected CRISPR components are shown to cause mosaicism in mouse embryos (Hashimoto & Takemoto, 2015; Hashimoto et al., 2016; Sato et al., 2015). However, injecting a high concentration of sgRNA/Cas9 may reduce embryonic viability (Midic et al., 2017).

Several approaches have been developed to improve efficiency and reduce mosaicism. However, it is important to remember that the frequency of mosaicism and possibly also the mechanism by which it occurs differ among species. Thus, approaches to decrease mosaicism in other species are not necessarily relevant for germline editing in humans. Apart from the different approaches to reduce mosaicism in embryos, mosaicism can be prevented by introducing the gene edit in gametes (sperm and eggs) or their precursors prior to fertilization (National Academy of Sciences, 2017).

The CRISPR/Cas9 components must be introduced at a very early-stage zygote to ensure that the gene-editing occurs before the first DNA replication. Persistent Cas9 cleavage activity after the one-cell stage of embryonic development will often create different modifications in every daughter cell and thus create a mosaic embryo (Chen et al., 2015; Mizuno et al., 2014; Niu et al., 2014; Xin et al., 2016; Yen et al., 2014). The double-stranded DNA break created by Cas9 will be repaired by either non-homologous end joining (NHEJ) or homologous direct

[9] Duchenne muscular dystrophy is a neuromuscular disease caused by mutations in the dystrophin (*DMD*) gene. The absence of dystrophin causes degeneration of muscle fibers and progressive muscle weakness with no current effective treatment (Emery, 2002; Fairclough et al., 2013).

repair (HDR), of which NHEJ is generally dominating in mammalian cells (Lieber, 2010; Mao et al., 2008). NHEJ causes random indels at the DSB site, and these indels will vary between the edited cells (Hsu et al., 2014). If a donor DNA template is present, the cells can repair the DNA with either NHEJ or HDR. This can result in some cells using HDR while other cells use NHEJ, thereby creating a mosaic embryo (Harrison et al., 2014; Hashimoto et al., 2016).

Cas9 activity after the one-cell stage of embryonic development occurs due to prolonged Cas9 activity or if the translation of Cas9 mRNA to functional Cas9 nuclease occurs after the first DNA replication (Hashimoto et al., 2016; Hsu et al., 2014; Mehravar et al., 2019). The latter is only a problem if Cas9 is delivered as plasmid or mRNA and can be prevented by using Cas9/sgRNA ribonucleoproteins (RNPs) (Aida et al., 2015; Burger et al., 2016; Hendel et al., 2015). Since fast delivery is essential to ensure that the edit occurs before the first DNA replication, electroporation is suggested to generate fewer mosaic embryos than microinjection (Hashimoto & Takemoto, 2015; Kaneko et al., 2014; Qin et al., 2015). By electroporating RNPs into early-stage embryos, Hashimoto et al. (2016) managed to generate non-mosaic mutant mouse embryos. However, this does not eliminate the mosaic problem because Csa9 cleavage activity can persist after cell division (Mehravar et al., 2019; Yen et al., 2014).

A remarkable study by Ma et al. (2017) showed a significant reduction in the occurrence of mosaicism when CRISPR/Cas9 components were co-injected with sperm into metaphase II oocytes[10]. The hypothesis is that the co-injection allows the gene editing to occur when the sperm still contains only one mutated copy of the gene. Additionally, it is believed that this extends the time of exposer to metaphase II (MII) cytoplasm, thereby allowing the CRISPR/Cas9 components to degrade before DNA replication takes place (Ma et al., 2017). Furthermore, Cas9 tagged with a ubiquitin-proteasome signal on N-terminus to reduce half-life is shown to decrease the occurrence of mosaicism without affecting the targeting efficiency in monkey embryos (Tu et al., 2017).

Increasing HDR:NHEJ ratio

Precise and efficient germline editing is highly contingent on HDR to repair the double-stranded DNA break, but low HDR efficiency is a major challenge in therapeutic use of CRISPR/Cas9-mediated gene editing. In addition to occur at a significantly lower frequency than NHEJ, HDR requires delivery of donor template DNA and is dependent on the cell cycle phase (Chapman

[10] This experiment require fertilization for research purpose alone. Embryo research in Norway (and probably other countries as well) are restricted to excess embryos, and fertilization of eggs for research purpose alone are prohibited.

et al., 2012; Maruyama et al., 2015). A study by Ma et al. (2017) showed that DSBs repair in human embryos occurs predominantly via HDR, suggesting that the DNA damage response system in embryos is different from that in somatic cells. However, NHEJ-induced indels were still reported (Ma et al., 2017). Development of approaches to improve HDR efficiency and reduce the frequency of error-prone NHEJ is therefore essentially important to ensure safe and efficient gene correction and gene knock-in.

Lin et al. (2014) found that since the choice between NHEJ and HDR is largely determined by the cell cycle phase, introducing RNPs into synchronized M-phase cells increased HDR efficiency from 9% to up to 33%. Furthermore, Nguyen et al. (2020) reported that adding a truncated Cas9 target sequence at the end of the donor DNA template increased HDR efficiency by approximately 2-4-fold when delivered as RNPs. HDR efficiency was further increased by stabilizing the RNP complexes with an anionic polymer (Nguyen et al., 2020). Double-nicking by paired Cas9 nickase (nCas9) to generate the double-stranded DNA break has also been shown to increase HDR efficiency (Ran et al., 2013; Xu et al., 2014). Another approach to increase HDR:NHEJ ratio is based on inhibition of NHEJ by targeting DNA ligase IV (a key enzyme in the NHEJ pathway) (Maruyama et al., 2015; Weber et al., 2015). However, DNA ligase IV deficiency is lethal in embryos, making it unsuitable for precise germline editing (Frank et al., 1998).

Technological improvements have enhanced HDR efficiency significantly, but obtaining a sufficiently high HDR:NHEJ ratio remains a considerable challenge in therapeutic gene editing. It is important to note that it is considerable differences in DNA repairs between human and rodent embryos and primates have higher rates of embryo chromosome instability than any other species (Vanneste et al., 2009). Furthermore, the response and ability to repair damaged DNA are not well understood in mammalian embryos (Khokhlova et al., 2020). Thus, research on animal embryos is considered insufficient to validate the safety of the process (Li et al., 2017).

Genotoxicity and large chromosomal alterations

Recent studies found that CRISPR/Cas9 editing can cause complex chromosomal rearrangements and deletions of large DNA segments or entire chromosomes (Alanis-Lobato et al., 2021; Leibowitz et al., 2021; Liang et al., 2020; Zuccaro et al., 2020). Double-stranded DNA breaks are highly toxic, and failure to repair the Cas9-mediated lesions can promote tumorigenesis and cause chromosome instability and cell death (Chapman et al., 2012;

Shrivastav et al., 2008). Hence, these findings underscore the necessity of more research before therapeutic use of DNA/Cas9 germline editing.

Zuccaro et al. (2020) found that half of the DNA/Cas9-mediated double-stranded DNA breaks remained unrepaired, resulting in loss of part of or whole chromosome. Alanis-Lobato et al. (2021) reported an increased frequency of chromosomal instability at the on-target site in CRISPR/Cas9 edited human embryos compared to non-edited early-stage embryos (Babariya et al., 2017; Vanneste et al., 2009). Analysis of a proportion of cells in the embryos showed that around 68 % of the targeted cells did not exhibit any chromosomal abnormalities (Alanis-Lobato et al., 2021). However, given the high frequency of mosaicism in germline-edited embryos, the embryos may contain cells with undetected chromosomal abnormalities. Furthermore, Leibowitz et al. (2021) found that CRISPR/Cas9 gene editing in actively dividing cells causes a significant increase in the formation of micronuclei and/or chromosome bridges that can initiate chromothripsis[11], which is highly associated with cancer and congenital disease (Cortés-Ciriano et al., 2020; Kloosterman & Cuppen, 2013; Liu et al., 2011; Ly et al., 2019; Rausch et al., 2012; Stephens et al., 2011).

Genetic pleiotropy

The human genome is ~3 billion base pairs long and consists of approximately 20 000 – 21 000 genes. Tremendous scientific progress in the past decade has dramatically improved our understanding of the human genome, but the complete functionality of all the genes in the genome remains elusive. In addition to most phenotypic traits being determined by multiple genes, some genes also affect multiple phenotypes – a common phenomenon called pleiotropy. Hence, we may know the function of a gene, but we may not know *all* the functions. Consequently, mutations in one gene may lead to unpredicted and unwanted changes in other phenotypic traits.

Li and Shen (2019) used the UK Biobank to investigate the nature of pleiotropy in relation to gene editing. Investigation of susceptibility loci for six complex human diseases[12], all of which showed evidence for pleiotropy, indicate that pleiotropic effects are ubiquitous (Li & Shen, 2019). They also studied the pleiotropic effect of *CCR5*[13], which is the gene He Jiankui targeted in an attempt to create HIV-resistant individuals. *CCR5* is proposed to be highly pleiotropic and associated with susceptibility and defense against several diseases (Cyranoski,

[11] Extensive chromosome rearrangements in a single event involving one or a few chromosomes.
[12] Breast cancer, lung cancer, coronary artery disease, type 2 diabetes, bipolar disorder, and major depressive disorder.
[13] See Chapter 1: Introduction (p. 2-3)

2018). The statistical analysis of CCR5 pleiotropy indicated that the CCR5Δ32 deletion gives an elevated risk of 30 out of 131 diseases (Li & Shen, 2019), supporting the many concerns that editing CCR5 does more harm than good.

Genetic pleiotropy complicates gene editing and poses a risk of unintended and potentially harmful effects on other phenotypes. It is thus important to consider the potential of pleiotropic effects before gene editing treatment. However, gene correction to restore the "wild-type" gene function is unlikely to cause any unexpected and harmful changes in other phenotypes. Hence, pleiotropy does not pose any significant risk when treating severe monogenic diseases like Tay Sachs and Huntington's disease.

Heterozygote advantage

When a genetic mutation that primarily causes disease or disadvantage persists in a population, it is assumed to have some sort of advantage. This *a priori* assumption is in line with Darwin's theory of natural selection, saying that individuals with advantageous traits are more likely to survive and reproduce. As Darwin wrote in *The Origin of Species* (1859 p. 126): "… as each selected and favored form increase in number, so will the less-favored forms decrease and become rare. Rarity … is the precursor to extinction". In other words, a merely disadvantageous mutation will eventually be wiped out from the population.

'Heterozygote advantage' is the phenomenon in which a heterozygous genotype is more advantageous than a homozygous genotype. This means that even though having two copies of a disease-gene is strongly disadvantageous, having only one copy of the disease-gene can increase the fitness of the individual relative to having no copy of the disease-gene. An example of this is the increased defense against mycobacteria in individuals with one copy of the Tay Sachs gene. Observations of a potential correlation between the frequency of the Tay Sachs gene and incidences of tuberculosis indicated some sort of advantage in defense against *Mycobacterium tuberculosis* in those carrying the Tay Sachs gene (Petersen et al., 1983; Rotter & Diamond, 1987). The hypothesis was later strengthened when studies revealed that carriers of the Tay Sachs gene have an increased expression of HexB (β-subunit of αβ-hexosaminidase), which is closely associated with increased host defense against mycobacteria (Koo et al., 2008; Withrock et al., 2015). Another example of heterozygote advantage is sickle cell anemia which has a protective effect against malaria infection (Croke et al., 2017; Williams et al., 2005). This may explain why carriers of sickle cell anemia are more common in some African and Asian populations.

Although heterozygote advantage does not pose any direct risk or challenge to germline editing, it should be included when calculating benefits and risks. Germline editing has the potential to eradicate heritable diseases, thereby abolishing the potential heterozygote advantage. This may impact entire populations as it will make the population more prone to other diseases, especially if the advantage is in defense against transmittable diseases such as tuberculosis.

CONCLUSION

CRISPR technology confers a promising potential for treatment and prevention of heritable genetic diseases and can thus save millions of people from tremendous pain and suffering. There are still some risks and technological challenges that must be surmounted before adopting germline editing for clinical applications, and some risks may not be discovered before clinical trials. However, the benefits might outweigh the risks in cases of catastrophic genetic diseases such as Tay Sachs. It is (in my opinion) justifiable and perhaps even a moral imperative to begin clinical trials in such cases despite some uncertainty regarding risks, for one thing is certain: the risk of not preventing certain diseases is inevitable fatal.

CHAPTER 4

DRAWING THE LINE BETWEEN THERAPY AND HUMAN ENHANCEMENT

The ethical attitudes towards CRISPR germline editing are largely dependent on whether it is seen in terms of therapy or as human enhancement. Human enhancement is a much-debated topic in the CRISPR debate and is usually used to refer to interventions that go beyond therapy. The prospect of using gene-editing technology to enhance human capacities is supported by some but is more often met with concerns and condemnation. Genetic interventions for the purpose of medical treatment, on the other hand, are often met with a more positive attitude. Although the concerns and criticism are also present when discussing germline editing as medical treatment, the benefits of removing harmful diseases are somehow easier to comprehend and, thus, easier to support and accept. Hence, a relatively common view is that CRISPR germline editing is acceptable *if* – and only if – it is for medical purposes to remove disease or disability (National Academy of Sciences, 2017)[14].

This view may seem perfectly reasonable at first sight; if there is a way to rescue people from disease, we should do it. However, this is also one of the most difficult aspects of the human germline editing debate because therapy and human enhancement are ambiguous and often overlapping terms. Although many genetic interventions can be rather intuitively classified as either therapy or enhancement, many possible genetic interventions lie within a problematic grey area where the line is blurry and constantly changing. Different interpretations on what qualifies as disease or disability and what counts as 'severe enough' to justify genetic intervention make room for ambiguity and inconsistency even within the same frame of reference. The constant change in our perception of disease creates additional difficulties. Increased knowledge about human biology and genetics improves our understanding of disease

[14] Numerous surveys have shown a clear difference in the public's attitude towards genome editing (both somatic and germline) and human enhancement. A summary of surveys is presented in National Academy of Sciences, National Academy of Engineering, National Academy of Medicine. (2017). *Human Genome Editing: Science, Ethics, and Governance*. Washington, DC: The National Academies Press. doi:10.17226/24623 (p. 140-43)

but may also change our perception of what is 'normal' and what is a disease. Development of new and improved medical- and technological inventions enables treatment of conditions formerly seen as 'normal' - and as soon as a condition can be treated, our perception of the condition is likely to change from 'normal' to 'a medical problem' (Elliott, 1999). Lisbeth Witthøfft Nielsen calls this a 'gradual medicalization process' and says that: "from this perspective, even aging can be seen as a disease or an imperfect aspect of being human that can be, if not cured, then at least treated for the purpose of living longer" (Nielsen, 2011 p. 26).

TERMINOLOGY

The lack of a clear consensus about the definition of human enhancement and the resulting lack of a distinction between human enhancement and therapy creates confusion and inconsistency in the germline editing debate that may compromise the establishment of an ethically justifiable regulatory framework. William Gardner wrote that "this line should be drawn, so humanity can reap the benefits of gene therapy without experiencing the risk of genetic enhancement" (Gardner, 1995 p. 66) but expressed worries about whether it is possible to draw a stable line between therapy and human enhancement. Numerous definitions of human enhancement have been proposed to attempt to draw this line but, as stated by Paul Root Wolpe: "… any exclusive enhancement definition must fail, in part because concepts such as disease, normalcy, and health are significantly culturally and historically bound, and thus the result of negotiated values" (Wolpe, 2002 p. 390).

However, in an attempt to avoid the inconsistency in definitions to impede the ethical debate, it is necessary to first specify where the line between therapy and human enhancement is drawn in this thesis. In order to do this, I will start by briefly discussing the terms 'disease', 'disability', 'therapy' and 'human enhancement'.

Disease

Most people have an intuitive idea of what a disease is. However, the establishment of a satisfying definition of disease that prevents underestimating harmful conditions without promoting over-diagnosis and over-treatment is a challenging task not yet accomplished. Resultingly, distinguishing between what is a disease and what is merely a condition or abnormality is not as straightforward as it may seem at first sight.

A disease can, in an oversimplified sense, be seen as the opposite of health. WHO defines health as "a state of physical, mental, and social well-being and not merely the absence of

disease or infirmity" (World Health Organization, 1948). However, this does not solve the problem because the definition of health is equally tricky. Alternatively, disease can be understood as a deviation from normal structure and functioning. Christopher Boorse introduced the 'species-typical functioning' account, in which disease is understood as "internal states that depress a functional ability below species-typical levels" (Boorse, 1977).

However, not all deviations from normal structure and function are considered a disease; deviations from normality can be seen as merely an abnormality or a normal human variation. It is therefore suggested that a definition of disease must include both dysfunction and harm, as in the definition formulated by Jerome Wakefield: "a disorder exist when the failure of a person's internal mechanisms to perform their functions as designed by nature impinges harmfully on the person's well-being as defined by social values and meanings" (Wakefield, 1992, as cited in Correia & Storanov, 2021).

Disability

The concept of disability is even more difficult to define than the concept of disease. The International Classification of Functioning, Disability and Health defines disability as "an umbrella term for impairment, activity limitations and participation restrictions" (World Health Organization, 2001). This rather broad definition will not be sufficient for deciding whether a particular 'condition' is a disability in the sense that it should be removed.

Most, and perhaps all, people have one or more limitations or impairments in their life without having a disability, and whether a particular limitation or impairment is a disability is often contingent on the environment and social context. For instance, as Richard Hull pointed out, the limitation and impairment caused by not being able to walk are dependent on the architecture of the environment because "if ramps and lifts were more common than stairs, then people who rely on wheels for locomotion would not be disadvantaged in their pursuit of the many and wide ranging activities that stairs prohibit" (Hull, 1998 p. 204).

The social and environmental impact on disability has raised questions about whether a disability is mainly caused by a social construct. However, if limitations caused by a social construct are a disability, can it be seen as a disability to, for instance, be a woman? Women are all too often faced with discrimination and inequality that can impair their chances for human flourishing. However, the limitations and impairment many women encounters have nothing to do with neither the gender itself nor functional limitation; the limitations are simply caused by a social construct that should have been abandoned a long time ago. Although the environment and social construct contribute to the impairment, it cannot be sufficient to define

disability. Jonathan Glover suggested that "disability requires failure or limitation of functioning. But a limitation of functioning creates disability only if (on its own or *via* social discrimination) it impairs capacities of human flourishing" (Glover, 2006 p. 17).

A disability is often seen as a deviation from normal functioning. However, there is some disagreement about the relevance of 'normal functioning' in defining disability because normal functioning is neither sufficient nor necessary to affect a person's life negatively. Loss of hearing is normal at old age, but the fact that it is normal does not make it any less disabling. Similarly, not all deviations from normality are a disability; a deviation from normality can sometimes be seen as merely a difference. Deafness is a deviation from normality that is commonly seen as a limitation, and most people would therefore agree that deafness is a disability. Many deaf people have, however, claimed that deafness is a difference rather than a disability. Whether a particular condition is a disability or merely a difference can in some cases only be seen through the eyes of those experiencing it. Hence, how individuals experience a condition should impact how the rest of us see it (Glover, 2006; Newell, 2003).

John Harris defines disability as "a condition that someone has a strong rational preference not to be in and one that is in some sense a harmed condition" (Harris, 2001 p. 384) where a 'harmed condition' refers to 'harm relative to possible alternatives' rather than 'harm relative to normal functioning' because people can be disabled despite having no deviation from normality. Savulescu and Kahane proposed a similar definition called 'the welfarist account', which defines disability as "a stable physical or psychological property of subject S that leads to a reduction of S's well-being in circumstances C" (Kahane & Savulescu, 2009 p. 19). The welfarist account differs from Harris' definition in that it does not imply that disability is a condition that should be changed/removed; removing the disability can avoid reduction of well-being but is not always necessary (Kahane & Savulescu, 2009).

Therapy

Therapy is the treatment of a disease or a deficiency to restore health or bring a diseased individual back to a 'natural human state' (Nielsen, 2011). The concept of therapy may seem straightforward, but the lack of consensus about what constitutes disease and health raises problems in defining an appropriate extent of therapy. The term 'medicine', which therapy often is seen as a part of, is sometimes defined in a way that includes 'improvement of health', such as in *Webster's New Twentieth Century Dictionary of the English Language,* which defines medicine as "science and art of diagnosing, treating, curing, and preventing disease, relieving pain, and improving and preserving health" (Webster, 1970). With this definition, genetic

engineering to improve certain human capacities such as physical fitness can be said to be medical because it will improve health.

Also, there are some objections to germline editing being characterized as therapy because the individual who could benefit or be harmed by the intervention does not exist yet. Since the individual does not exist, neither does the disease. Germline editing is, therefore, more correctly seen as *prevention of disease* rather than *treatment of an existing disease* (Glannon, 2003). However, this is not equivalent to saying that all germline editing being enhancement; if germline editing cannot be seen as therapy because the person does not exist yet, it cannot be human enhancement either. Since zygotes and embryos lack the capacity for mentality, they are not persons, and neither benefit from nor be harmed by the germline editing. Nevertheless, since zygotes and embryos are *potential* persons, the person they develop into can benefit from or be harmed by the intervention.

Human enhancement

One of the main issues in establishing a line between therapy and enhancement is the fact that the term *enhancement* has different meanings for different persons. Whereas some view enhancement as a quantitative *increase*, others claim that enhancement is best seen in terms of a qualitative *improvement* or *betterment*. The problem with defining enhancement is far from new; the term has pervaded bioethics debated for several decades. In 1998, Erik Parens wrote that

> … some participants think the term *enhancement* is so frightened with erroneous assumptions and so ripe for abuse that we ought not even use it. My sense is that if we didn't use enhancement, we would end up with another term with similar problems (Parens, 1998 p. 2).

Numerous definitions of human enhancement have been proposed but have more often than not exacerbated the confusion rather than solved the issues the term elicits. Nonetheless, human enhancement in bioethics is most commonly seen in terms of 'non-medicine' or 'beyond therapy', where it refers to "any kind of genetic, biomedical, or pharmaceutical intervention aimed at improving human dispositions, capacities, and well-being, even when there is no pathology to be treated" (Giubilini & Sanyal, 2016 p. 1). Although seemingly comprehensible, the distinction between human enhancement and therapy is still unclear. Consider the following case of increasing IQ:

Case 4: Increasing IQ

(*Note that this case is highly hypothetical. The genetic basis for intelligence is not found, so even if CRISPR could in theory be used to edit "intelligence-genes", our knowledge of these genes is far from sufficient*).

Imagine that we have a technology that can increase intelligence and thus cure intellectual disability. An IQ score between 90-109 is regarded as average, whereas an IQ score below 70 is generally regarded as an intellectual disability (Lee et al., 2019). Is genetic intervention to increase IQ therapy or human enhancement? At what level does it go from 'medical treatment' to 'human enhancement'?

Christopher Boorse's species-typical functioning account of disease implies that medicine becomes an enhancement if the intervention increases species-typical normal functioning beyond a statistically defined species-typical level of functioning. Nick Bostrom has proposed a similar account. He holds that human enhancement is "an intervention that improves the functioning of some subsystem of an organism beyond its reference state: or that creates an entirely new functioning or subsystem that the organism previously lacked" (Bostrom, 2008 p. 179). The reference state is not explicitly defined, but Bostrom (2008) points out that the reference state can be defined as "the state that is normal for some particular individual when she is not subject to any specific disease or injury" (p. 179) or it can refer to a species-typical level of functioning (Bostrom, 2008).

However, it is not necessarily clear how to define the level of species-typical. One alternative is to define the level as the "bottom-line" of species-typical functioning by calculating the level at which only a small fraction (e.g., between 1-10%, depending on the distribution of the trait) of the population is below this level. However, it is questionable whether it can be seen as "species-typical" if it relates to only 1-10% of the species members, whereas the remaining 90-99% have a higher level of functioning. Thus, it may be more appropriate to define the level for species-typical functioning based on the average level of function.

Case 4: Increasing IQ – The species-typical normal functioning account

The bottom-line level of species-typical functioning holds that interventions to increase IQ up to 70 is therapy, but an intervention that increases IQ above this level is human enhancement.

The average level of species-typical functioning holds that an increase in IQ up to average IQ level (~100) is therapy, whereas any increase above the average IQ score is human enhancement.

One problem with the species-typical normal functioning account is that it views human enhancement as a *quantitative* increase of functioning rather than a *qualitative* improvement. The 'normal' is thus presumed to be 'better', although this is not always the case. Therefore, it has been suggested that a definition of human enhancement should be based on the intervention's qualitative value (e.g., increased well-being). One such definition of human enhancement is derived from the welfarist definition of disability. The welfarist definition holds that human enhancement is "any change in biology or psychology of a person which increases the chances of leading a good life in the relevant set of circumstances" (Savulescu et al., 2011 p. 7). The welfarist account acknowledges that 'normality' is not always beneficial and view enhancement as 'betterment' rather than an 'increase'.

Case 4: Increasing IQ – The welfarist account
Any intervention that increases IQ is human enhancement if it increases the person's well-being.

The welfarist account does not distinguish between therapy and enhancement; medical treatment is considered human enhancement as long as it increases well-being. Hence, medical procedures and treatments such as vaccines, growth hormones, ADHD medication, etc., are seen as human enhancement. Even medicine in general, education, diet, and exercise may fall under the category of human enhancement because, when all comes to all, its purpose is to improve human capacities in some way or another.

DRAWING THE LINE

As demonstrated in this chapter, the line between therapy and human enhancement is difficult, perhaps even possible, to define. For the sake of avoiding the many different definitions and conceptions to interfere with the following ethical discussion, I will in this thesis use a version of Boorse's 'species-typical normal functioning' account that focuses on the genetic basis of the trait rather than the phenotypic expression of the trait.

> **The normal gene function account:** Therapy refers to the correction of gene mutations to restore the gene's normal function (i.e., restore a mutated gene back to wild-type, whereas human enhancement refers to editing genes where there are no mutations to be corrected.

The 'normal gene function' account will require that the trait's biological basis is known in order to evaluate whether it is therapy or enhancement. This may allow for a more sensible debate on germline editing because the evaluation of the obvious cases of therapy (where a known mutation cause disease, such as in Tay Sachs and Huntington's disease) will not be debilitated by judgments about the cases where there is no known mutation to correct. Also, the normal gene function account may provide a more accurate risk assessment because many of the risks involved in gene editing (such as pleiotropy and sgRNA-dependent off-target mutation) are associated with specific genes or gene sequences.

Case 3: HIV resistance – The normal gene function account

A 32 bp deletion of the CCR5 gene (termed CCR5Δ32) gives resistance to HIV due to mutations in the receptor HIV virus is dependent on to enter the red blood cells. ~1% of Northern European populations are born with the CCR5Δ32 variant and are thus resistant to HIV. However, germline editing to create HIV resistance inactivates normal gene function and is, therefore, human enhancement.

The requirement for a known biological basis put some limitations on the applicability of this account. Most characteristics (phenotypes) are determined by a complex genetic pathway with multiple genes acting together. These traits will perhaps be easier to evaluate with the species-typical normal functioning account. That being said, the biological basis of a trait must be well-known in order to make deliberate changes in the trait. Another weakness of the normal gene function account is the fact that normal gene function is not always beneficial due to 'heterozygote advantage', the phenomenon where having one copy of a gene give some sort of advantage (see Chapter 3). For instance, having one copy of the sickle cell anemia gene give some protection against malaria infection and is therefore beneficial in areas with high prevalence of malaria. Nonetheless, despite the flaws with the normal gene function account, it is sufficient for the purpose of this thesis.

CHAPTER 5

ETHICAL ISSUES WITH HUMAN GERMLINE EDITING

The previous chapters have focused on the technological aspect of potential risks involved in germline editing with CRISPR/Cas. However, safety is far from the only concern when it comes to making changes in the human germline. The heritable nature of changes in the germline raises concerns about the consequences it may have for the existing population and future generations. These concerns are based on the broader consequences of germline editing on society and humanity rather than the biotechnological risks. In order to focus on these consequences, the rest of the thesis is therefore written on the assumption that the challenges and risks involved in germline editing are surmounted and that the technology is safe, or at least safe enough, to be used for clinical applications.

One of the most prevalent arguments against germline editing is the so-called 'slippery slope', which in general terms holds that allowing any type of germline editing will eventually lead us to cross an ethical boundary. The slippery slope arguments are often followed by scary prospects of eugenics and 'designer babies' as an inevitable result of allowing germline editing. These predictions of catastrophic outcomes are, however, often based on speculation and assumption rather than evidence. It is therefore dubious if they are sufficient to justify a ban.

Many have raised concerns over how allowing germline editing may affect society; that it will widen the gap between 'the rich and the poor', increase discrimination and reinforce unjust social norms. Disability rights advocates have expressed objections to using technology to avoid having a child with a disability and claim that the signal it sends contributes to upholding discrimination and problematic misconceptions about the quality of life for people with disabilities (Asch, 1999; Saxton, 2000). Many have, however, argued that there are better methods to eradicate discrimination against disabled people and that one can opt for having a child without disability without devaluing people with disabilities (Glover, 2006; Savulescu, 2001). It has also been argued that germline editing can level the playing field and thus decrease inequality.

The thought of making deliberate changes in the very foundation of what makes a human being *that exact* human being invokes strong emotions. Much attention is given to how human germline editing can affect the individual, society, and the human species. The 'nature versus nurture' debate is arguably centuries old, but it is now accepted by most that it is more correctly seen as 'nature *and* nurture'. Hence, *who you are* is a result of both genetics (nature) and environment (nurture). However, to what extent genetics influence identity and personality remain uncertain. Thus, whether a germline edited person will have a different personal identity due to the changes in DNA cannot be said with absolute certainty. It has also been proposed that it may affect an individual negatively to know that their genetic characteristics have been intentionally altered by another person. Jürgen Habermas suggested that manipulation of the human germline can impair the individuals' autonomy and relation-to-self, as well as compromise the ethical self-understanding of the species (Habermas, 2003).

> For as soon as adults treat the desirable genetic trait of their descendants as a product they can shape according to a design of their own liking, they are exercising a kind of control over their genetically manipulated offspring that intervenes in the somatic bases of another person's spontaneous relation-to-self and ethical freedom (Habermas, 2003 p. 13).

There are undeniably many important factors to consider when establishing the ethical guidelines for human germline editing. However, the obscurity and speculation around many of these concerns make them challenging to evaluate by placing additional uncertainties in the ethical minefield of human germline editing. Some of the concerns about germline editing are based upon hypothetical prophecies of a potential – but as we will see, often unlikely – dystopian future. The problem with this is that we risk banning a highly beneficial technology based on speculation about what may or may not happen. In other words, we risk failing to save lives based on unjustifiable reasons.

The fact that many of the arguments can be used both to object and support germline editing perturbs the debate even further. This is particularly obtrusive when discussing inequality, autonomy, and the right to an open future. Whether the argument is perceived as *pro*-gene editing or *anti*-gene editing depends on the particular application and purpose of germline editing, as well as the subjective interpretation of the argument in question.

DOWN THE SLIPPERY SLOPE

One of the most prominent arguments against germline editing is the so-called 'slippery slope argument'. Different versions of the slippery slope argument have been proposed, of which the empirical version and the conceptual version are the most prevalent in the germline editing debate. Common for these versions is that allowing a morally neutral A will eventually lead to allowing a morally unacceptable B. A third version of the slippery slope, the arbitrary result version, holds that allowing A will lead to a morally uncontrollable situation. The slippery slope arguments are widely used to warn against the consequences of allowing germline editing, where the proposed catastrophic end is often related to eugenics programs, 'designer babies', and increased inequality. According to John Rifkin, gene editing should not be allowed because:

> Once we decide to begin the process of human genetic engineering, there is really no logical place to stop. If diabetes, sickle cell anemia, and cancer are to be cured by altering the genetic makeup of an individual, why not proceed to other 'disorders': myopia, color blindness, lefthandedness? Indeed, what is to preclude a society from deciding that a certain skin color is a disorder? (Rifkin, 1983 as cited in Fletcher, 1985)

The empirical slippery slope

The empirical version claims that if we allow a morally neutral A, we will eventually allow a morally unacceptable B because the relevant moral distinction between A and B is not sufficient to influence our choices (Gardner, 1995; Launis, 2002). The empirical slippery slope argument is based upon the proposition that allowing some forms of gene editing will lead to changes in our morality and ability to make ethically justifiable decisions. As soon as the very first change is made, there is no way back because the initial change will somehow 'promote' additional changes. Technology can, in that sense, be said to be self-reinforcing because employment of the technology will encourage further employment and adaption of that technology (Gardner, 1995).

One of the concerns is that the employment of germline editing for therapeutic purposes will change our perception of health and disease and that this change will cause us to eventually use germline editing technology to change genetic characteristics we today see as normal. The changes in our perception of normality and disease (or any other subject of matter) usually occur at a sufficiently slow rate to go unnoticed, in addition to the changes often being *small enough* to be regarded as insignificant when considered separately. The fear is that by the time

we notice the changes, the catastrophic end is already present, or at least too close to avoid. However, proponents of this argument seem to fail to acknowledge that our perception of disease and disability is constantly changing as scientific progress continuously extends our knowledge and possibilities in the medical field (as mentioned in Chapter 4). These changes are not used to stop scientific research in other areas – the benefits are simply too great.

William Gardner argues that we cannot stop the slippery slope because a prohibition of human enhancement is likely to fail as it will be "undermined by the dynamics of competitions among parents and among nations" (Gardner, 1995 p. 69). As soon as some people begin enhancing their children, the attractiveness of human enhancement – or, perhaps more correctly, the disadvantage of *not* being enhanced – will increase, and more people will thus have the desire to enhance their children's characteristics. This may even cause parents, who initially would have rejected germline editing, to feel pressured to enhance their children's genes to prevent them from being 'disadvantaged' compared to the children with enhanced traits. Thus, as soon as the prohibition fails, the 'level' of human enhancement will increase exponentially as more and more people employ germline editing to enhance their children. Gardner called this an "avalanche slope – a surface that may remain stable for a time but is liable to random, sudden, and catastrophic collapse" (Gardner, 1995 p. 79)

Furthermore, as Gardner (1995) stated, a prohibition of human enhancement is not only vulnerable to personal choices and parental competition, but it is also vulnerable to different nations having different regulations. Legalization of genetic engineering in one country will probably lead to legalization in other countries. One reason behind this is 'genetic tourism', where people from countries where genetic engineering is forbidden travel to countries where it is has been legalized. This is already a prevalent practice in medical treatment and cosmetic procedures. To ban gene technology in some countries while allowing it in others will consequently be ineffective. Other reasons for other counties to legalize germline editing would include advancement of the nation. This may seem like an absurd and implausible reason, but if a country begins to genetically engineer its population to increase intelligence, for example, eventually, within a generation potentially, this could lead to a more effective and capable workforce. Consequentially, other countries may have to permit genetic engineering in order to compete internationally.

The conceptual slippery slope

The conceptual version of the slippery slope (also called the logical slippery slope) holds that once we allow a morally neutral A, we are permitted to allow a morally unacceptable B because

there is no clear distinction between A and B, and we should therefore not allow A (Gardner, 1995; Launis, 2002). The conceptual version of the slippery slope can be based on either consistency or continuum (Launis, 2002).

The consistency-based version states that there is no conceptual difference between A and B, and allowing A will therefore mean allowing B, although B is seen as unacceptable. In other words, this argument says that we cannot allow therapeutic germline editing if human enhancement is ethically unacceptable because of the lack of conceptual difference between therapeutic germline editing and human enhancement. However, this argument is invalid because, as we saw in chapter 4, it is possible to argue for a conceptual difference between therapeutic germline editing and human enhancement. How to define this difference is indeed disputed, but that does not change the fact that there are conceptual differences. The difference between therapy and human enhancement can, for instance, be in terms of normal gene function where correction of a genetic mutation to restore the normal gene function is therapy, whereas editing a gene where there is no abnormal mutation to correct is human enhancement.

Furthermore, the consistency-based argument seems in some sense implausible because if there really is no relevant conceptual difference between therapeutic germline editing and human enhancement, how can it then be that therapeutic germline editing is acceptable, whereas human enhancement is not? If allowing therapeutic germline editing means that we are permitted to allow human enhancement as well due to the lack of a conceptual difference, one cannot say that human enhancement is unacceptable because that will mean that also therapeutic germline editing is unacceptable. Thus, one has to choose between (1) both therapeutic germline editing and human enhancement are acceptable, or (2) both therapeutic germline editing and human enhancement are unacceptable. Regardless of whether one chooses alternative 1 or 2, the initial argument becomes nonsensical. With alternative 1, there is no problem in allowing therapeutic germline editing because human enhancement is also accepted, whereas with alternative 2, therapeutic germline editing is not accepted and will therefore not be allowed, and the initial argument thus becomes irrelevant.

The continuum-based version, on the other hand, acknowledges that there is a relevant difference between A and B, but the continuum of intermediate steps between them makes it impossible to draw a meaningful moral line between A and B, and we will therefore eventually be committed to allow B if we allow A (Launis, 2002). In other words, we cannot allow therapeutic germline editing because the line between therapy and enhancement is too vague to distinguish between them. This reasoning has, however, met some criticism. Nils Holtug (1993) stated that:

> Maybe there is a grey zone where we are not sure whether or not gene therapy would be morally responsible, but then there would also be cases where we were sure that it was. If this is the case, why can't we just draw a line while making sure that if we err, we err on the side of safety? (p. 410)

I will again emphasize the necessity to evaluate every possible application of CRISPR individually. There will always be some cases in the grey zone, but that should not prevent us from helping those who are worst off. To say it in other words, just because there are some disagreements over whether conditions such as deafness is a disability that should be removed or not, we should not refuse to help those who, without germline editing, will not get the chance to live a good life. The safety line can, for instance, be drawn by using the normal gene function account (see Chapter 4) and Quality of life assessments (see Chapter 6) to evaluate what conditions qualify as severe disease.

The arbitrary result slippery slope

The arbitrary result version of the slippery slope holds that once we allow A, we will end up in a morally uncontrollable situation where we must make new moral judgments and principled decision about what factors that should be made morally relevant in order to retain ethical consistency (Launis, 2002). However, since the situation is new and we do not have a sufficient understanding of the potential consequences, the result will be more or less arbitrary and are likely to have unexpected consequences. As soon as the decision is made on how to proceed, we will again find ourselves in an entirely new situation where we again must make new moral judgments and decide what is morally relevant. Thus, "along with this decision, we step on a slippery slope from which we cannot non-arbitrarily get off, since we have no idea what else we are thereby committed to accepting" (Launis, 2002).

The arbitrary result slippery slope does not object to germline editing because allowing it will lead to an inevitable catastrophic end but because it is impossible to know what the ending will be. Germline editing can indeed have unpredicted consequences, but as mentioned in previous sections, the consequence of not using germline editing to prevent genetic diseases is, in some cases, such as Tay Sachs disease, catastrophic. The arbitrary result slippery slope does not provide sufficient substantiation to justify a ban on therapeutic germline editing, although the risk of unexpected consequences emphasizes the need to proceed with caution.

The new eugenics

The fear of a new era with eugenic policies has pervaded the germline editing debate and is often considered the inevitable catastrophic end in slippery slope arguments. The literal meaning of the word eugenics is 'good birth', which does not in itself imply something bad – in fact, it suggests something all prospective parents should wish for. The historical connotations, however, link eugenics to the horrors of the Nazi Reich, and eugenics is consequently deemed by many as something inherently bad.

> Undoubtedly, we have an obligation never to forget the Holocaust, or to allow history to repeat itself. Yet intuitively we have some moral obligation to promote good births—to have, in the most literal sense, eugenic aims. Indeed, if parents are encouraged to provide the best environment for their children (good nutrition, education, health care, a loving family situation, etc.), why not also encourage them to ensure their children have good genes? (Goering, 2014)

Eugenic policies were popular in several countries, including Germany, Sweden, the United States, and Britain, in the first half of the twentieth century. The aim was to improve the population's health, and the idea was based upon the fallacious assumption that every phenotypic trait was determined by a single gene. The strong genetic determinism was often extended beyond bodily characteristics: social phenomena such as poverty and criminality were thought to be determined by genetics and that these phenomena thus could be inherited. This led to the practice of encouraging some people to have more children (known as 'positive' eugenics), whereas others were encouraged not to have children (known as 'negative' eugenics) with the aim of 'improving' the genetic pool in the nation. The encouragement not to have children went as far as coercive sterilization and even murder (as in the Nazi eugenics) of the people who had – or were assumed to have – the 'wrong kind' of genes.

> Reprehensible as much as of the eugenic program was, there is something unobjectionable and perhaps even morally required in the part of its motivation that sought to endow future generations with genes that might enable their lives to go better. We need not abandon this motivation if we can pursue it justly (Buchanan et al., 2000 p. 60)

The term 'liberal eugenics' has been introduced as a type of 'new' eugenics based on freedom of choice and procreative liberty, as opposed to the coercive programs on which the 'old' and 'authoritative' eugenics were based (Agar, 2004). Advocates for liberal eugenics

recognize the benefits of genetic enhancement and claim that parents should be permitted to choose their children's genetic makeup, as long as it is within certain boundaries[15] (Agar, 2004; Glover, 2006; Green, 2007). Some even go as far as to state that it is a moral obligation (Savulescu, 2001; Savulescu & Kahane, 2009). Liberal eugenicists claim that there are several ways in which liberal eugenics differ significantly from the 'old' eugenics. First and foremost, liberal eugenics is based upon a more accurate understanding of genes as contributive rather than deterministic. The 'old' eugenics relied on a principle of strong genetic determinism that we today know is false for the vast majority of phenotypic traits[16]. Secondly, liberal eugenics is about the *individual* rather than 'the race'. The aim is to increase freedom of choice and well-being for the individual (the future child and the family), in contrast to authoritative eugenics that aimed at creating better humans to improve the human species and secure survival of the race. Although it can, to some extent, be argued that the goal of liberal eugenics is to remove certain 'undesirable' genes from the gene pool, the 'undesirable' genes that will be removed are primarily genes that cause harm.

Liberal eugenics have been widely criticized, and some have argued that the alleged differences between 'liberal' and 'old' eugenics are small (De Melo Martin, 2004; Sparrow, 2011). Many have expressed concerns for how liberal eugenics will affect society and argues that it will increase inequality and discrimination[17], especially with regards to discrimination of people with disability (Asch, 1999; Saxton, 2000). Others have argued that it may have profound consequences for the child's self-understanding and ability to create its own future[18] (Habermas, 2003). A genetically manipulated child risks being seen as a 'product of design' rather than a person, and the child "may bear the burden of living up to the standards he was 'designed' to meet" (Kass, 2003 p. 55).

> Eugenic interventions aiming at enhancement reduce ethical freedom insofar as they tie down the person concerned to rejected, but irreversible intentions of third parties, barring him from the spontaneous self-perception of being the undivided author of his own life… Only in the negative case of the prevention of extreme and highly

[15] There is a general agreement that the intervention should not cause harm, but the boundaries beyond that vary. This will be discussed in *Chapter 6: Choices and obligations when creating a child*.
[16] The vast majority of genes are *probabilistic* rather *deterministic,* meaning that having a certain gene can increase the possibility of a specific phenotypic trait but does not necessarily mean that the individual will develop the specific trait.
[17] Discussed in the next subchapter, *Increasing inequality and discrimination*.
[18] Discussed later in this chapter under *Personal identity and self-creation*.

> generalized evils may we have good reasons to assume that the person concerned would consent to the eugenic goal (Habermas, 2003 p. 63)

Irrational fear or sufficient to justify a ban?

Slippery slope arguments are widespread in the human gene editing debate, and the prospects of eugenics and an inevitable catastrophic end have raised profound concerns regarding the moral permissibility of gene technology. However, the validity of the slippery slope arguments has been questioned by a number of philosophers,[19] first and foremost due to the lack of substantiation. Other reproductive technologies such as preimplantation genetic testing (PGT) have been met with similar objections based on the same scary prospects. However, as argued by Alta Charo, the fact that allowing PGT did not lead to 'reckless' and immoral use of the technology indicates that the fear is somewhat irrational (Charo, 2017).

Thus, the fact that gene technology *can* be used for morally unacceptable purposes does not mean that allowing gene technology *must* lead to morally unacceptable use of the technology. The arguments saying that allowing germline editing will lead to an inevitable catastrophic end are speculative at best. Given the enormous benefit of germline editing, it cannot be justifiably prohibited based only on speculations about what may or may not come true – especially when there is little or no evidence that the catastrophic end will actually occur.

The dangerous fear of designer babies

The term 'designer baby' is defined as a baby whose genes have been chosen or manipulated in order to gain desirable traits and avoid disadvantageous traits such as genetic diseases. This definition is in itself problematic because it disregards both the purpose and circumstance of genetic intervention. As discussed in previous chapters, genetic intervention should not be assessed in general terms, as each case differs significantly in both purpose and circumstance. Also, the word 'design' is inapt and maybe even damaging to the germline editing debate due to our tendency to subconsciously associate 'design' with something aesthetic. Nevertheless, the word 'design' is frequently used in the context of germ editing.

Earlier this year, a high school teacher handed out a science assignment on biotechnology and gene technology, where one of the questions was about a future of 'designing babies'. The purpose of the question was to elicit curiosity and initiate debate, which it successfully did.

[19] See for example Berger, Edward M. & Gert, Bernard M. (1991). Genetic disorders and the ethical status of germ-line gene therapy. *The Journal of Medicine and Philosophy,* 16(6): 677-683; Holtug, N. (1993). Human Gene Therapy: Down the Slippery Slope?, *Bioethics*, 7: 402–419; Govier, T. (1982). What's Wrong with Slippery Slope Arguments?, *Canadian Journal of Philosophy*, 12: 303–316.

However, in the absence of accompanying questions focusing on the more realistic potential with gene technology, it risks giving a fallacious image of the possibilities with gene technology. Although it is explicitly expressed that the question is imaginary, it gives a good example of how the word ‘design’ can impair the ethical debate on germline editing by promoting misconceptions and misfocus. The question was formulated as follows:

> Imagine a future where parents can use gene technology to "design" children, meaning that they can bring into existence a child with artificially changed genes that will give them a child with the exact appearance and characteristics of the parents' preference. What is your opinion about such a future society? (Anonymous high school teacher, 2021)

The first problem with this thought experiment is that it falsely presupposes genetic determinism. The high level of complexity of the human genome makes it impossible to guarantee an outcome with exact characteristics. Although monogenic phenotypes can be changed with a relatively high degree of certainty, this is far from the case in polygenic traits. Complicated inheritance patterns and complex genotype-phenotype correlations – including the collective effect of all the genes, the phenotypic effect of gene interactions (epistasis), and environmental factors influencing gene expression – make it difficult to distinguish the phenotypic effect of individual genes. Consequently, prediction of resulting phenotypic outcome from polygenic germline editing is particularly challenging, which make it impossible to "design" a human being with specific changes in polygenic phenotypes.

The second pitfall is that it diminishes the huge potential for life-saving medical treatment by placing the focus on changing rather superficial cosmetic traits and characteristics. The cosmetic traits and characteristics are almost exclusively polygenic, which makes it highly impracticable to change. Many genetic diseases are, on the other hand, monogenic and thus far more achievable to change. In other words, instead of focusing on the actual realistic potential to save lives, the focus is on the not yet feasible possibility to decide our children’s esthetics. This, together with the fact that none of the accompanying questions in the science assignment mentioned the potential CRISPR/Cas has for medical treatment, can create a false impression of the potentiality and benefits of gene technology.

Heedless use of the term ‘designer baby’ pollutes the gene editing debate with misconceptions that trigger the development of ungrounded fears. Our tendency to subconsciously associate ‘design’ with something superficial and cosmetic strongly exaggerates the fear by undermining the potential to cure severe and fatal diseases. The realistic

potentiality to save human lives is somehow drowned by a fear of something hypothetical and currently unachievable. The irrational fear is grounded upon a fallacious assumption that the implementation of germline editing in clinical practice will instrumentalize reproduction to a point where children are products rather than persons.

> The more ruthless the intrusion into the makeup of the *human* genome becomes, the more inextricably the clinical mode of treatment is assimilated to the biotechnological mode of intervention, blurring the intuitive distinction between the grown and the made, the subjective and the objective – with repercussions reaching as far as the self-reference of the person to her bodily existence (Habermas, 2003 p. 47).

The fear is aggravated by the slippery slope argument implicating that allowing germline editing will lead to an inevitable dehumanization. Resultingly, human germline editing risk being deemed as something that must be avoided at all costs. The fact that germline editing might be the only chance of a long and pain-free life for some people is devalued for the sake of the "greater good". The problem is, however, that this creates a paradox where we must abstain from germline editing to avoid dehumanization, but by abstaining from germline editing, we may neglect humanity by failing to save people from suffering and potentially death.

The idea of a dehumanized dystopian future where parents can *order* babies with specific characteristics, specifically and deliberately designed to fit any preference the parents might have, is undoubtedly unpleasant. However, what some people seem to forget is that the likelihood for this to become a reality is marginal. Even though we now have the ability to make specific edits in the DNA and thereby change certain characteristics of human beings, the changes are so far limited to simple, monogenic traits. Our current understanding of genotype-phenotype correlations is far from sufficient to change the vast majority of genetic traits.

DISCRIMINATION AND INEQUALITY

Many have raised concerns regarding the effect germline editing may have on society. It has been suggested that germline editing can exacerbate existing problems with discrimination and prejudice, and many fear that allowing germline editing may increase inequality and injustice (Resnik, 1994). Disability rights activists have argued that to remove or select against disability sends a negative signal that a life with a disability is of less value (Asch, 1999; Saxton, 2000). Others have argued that unequal distribution of germline technology will increase the

polarization between the 'rich and poor' (Glover, 2006). However, germline editing technology may also be used to promote equality. Genetic disadvantage (meaning genetic disease and disability) need no longer be seen as an irremediable 'natural inequality', and it is therefore suggested that germline editing should be used to 'level the playing field' (Buchanan et al., 2000)

Stigmatizing disability

People with disabilities are met with stigmatization and discrimination every day, and many have expressed worries about how allowing germline editing will affect the people who are already disabled. Assumptions that disabilities have a severe negative effect on the quality of life and that it may even make life barely worth living are common among 'non-disabled people'. Although research on life satisfaction of people with disabilities has shown otherwise, disability is commonly seen as something predominantly negative even among health care professionals (Parens & Asch, 2000 p. 20). Jane Campbell, a British disability rights campaigner with muscular atrophy, wrote an article about how health care professionals assumed that "her life was barely worth living" and that the doctors had told her on two separate occasions that they assumed that she would not want life-saving treatment if she fell unconscious (Campbell, 2003). Frightened about what might happen to her, Campbell kept herself awake for 48 hours. Her husband stuck a photo of her in her graduation gown on the bedhead to remind the hospital staff that she was more than just the "shriveled form they saw lying in front of them" .

Wrongful assumptions and ugly attitudes towards disability have already put a certain level of pressure on women to not have children with disabilities. Some women have reported that health care professionals have tried to persuade them into prenatal diagnostic testing and termination of the pregnancy if the fetus has a disability (Paschoud, 2003). The concern is that the possibility of using CRISPR to remove disability may increase the already existing pressure to *not* have a child with disability or disease. Carson Strong suggested that if parents can control the characteristics of their children, they "might be less willing to accept the shortcomings of their children" and that "there would be a greater tendency to blame parents for their children's imperfections" (Strong, 2001 p. 13). Similar concerns have been proposed by Jürgen Habermas:

> Each new authorization of a prenatal therapeutic genetic intervention constitutes a tremendous burden for those parents who have principal reasons for not wanting to make use of the license. Whoever deviates from a permitted or even a familiarized eugenic practice, and takes the risk of an avoidable birth defect into the bargain, has

> to fear accusations of neglect, and possibly the resentment of their own child (Habermas, 2003 p. 91)

If that is so, that the pressure not to have a child with disability increases, does that imply that the lives of people with disability and disease have no value and that their life is a 'burden for society' that should be prevented at any cost? And will it increase the already existing stigmatization and discrimination of people with disabilities? Adrienne Asch (1999) has argued that we should change society's view of disability rather than changing the individual because "many of the supposed limits and problems associated with disability are socially, rather than biologically, imposed" (Asch, 1999 p. 1653). Clare Sainsbury, who wrote the book *Martian in the Playground* about what it means to be a person with Asperger's syndrome, expressed objections to the 'philosophy of normalization' because it signals that what disabled people often see as a mere difference is something that needs to be cured. She wrote that " 'normal' people take it as a basic human right to be accepted as they are, while the rest of us are viewed only in terms of what will make us more acceptable to them" (Sainsbury, 2000 as cited in Glover, 2002, p. 14).

But 'normality versus abnormality' cannot be what counts. A deviation from normality is neither sufficient nor necessary for a condition to be a disability. The important factor is whether a condition leads to a reduction in well-being and human flourishing. Given that many disabilities can cause limitations and impairments that can reduce well-being and human flourishing, is it wrong to aim to have children that do not have any disability? As Glover (2006) put it: "Is it right to have less flourishing children in order to avoid sending an undesirable signal to other people?" (p. 32).

It does not follow from the removal of a disability in one individual that people with the same disability are of less value. The disabled person *has* a disability, but the disabled person *is not* the disability. What it thus says is that disabilities more often than not lead to *less good* lives and should therefore be removed in order to give the child the best chance to flourish. To aim for a child with a 'better' potential to flourish is not based on prejudices against people with disabilities. As several writers have pointed out, there are better methods to decrease inequality and discrimination (Resnik, 1994; Savulescu, 2001).

> Even if the Disability Discrimination Claim were true, it would be a drastic step in favor of equality to inflict a higher risk of having a child with a disability in a couple (who do not want a child with disability) to promote social equality (Savulescu, 2001 p. 423).

One should, however, be cautious about the signal it may send if relatively drastic measures are used to avoid having a child with a disability. Actions must be taken in order to reduce the influence this may have on disabled persons sense of being valued. Thus, it must be explicitly stated that the removal of a disability in one individual does not mean that people with the same disability are of any less value. Glover (2006) describes two ways of which we can reduce the negative impact removal of disability can have on disabled persons. The first way is to draw a parallel to other medical treatments to make it clear that it is the condition that is undesirable – not the person who has it. Another way to reduce the negative impact is to be equally concerned with other factors that impair human flourishing, such as "poverty, bad housing, or child abuse" (Glover, 2006).

Increasing inequality

Social inequality is already present in all (or at least most) societies, and many have raised concerns that gene editing will exacerbate this already existing inequality (National Academy of Sciences, 2017). The germline editing technology is likely to be unequally distributed. Health care resources are far from equally shared between rich and poor countries, and it seems unlikely that it will be any different with gene technology. Genetic diseases may thus become something that only exists in developing countries, while the harmful and disadvantageous genes get eradicated from the gene pool in wealthy populations. This does not justify abstaining from therapeutic germline editing. Equal distribution of health care resources between countries should be promoted, but there are better ways to do this than by prohibiting health care in rich countries. The risk of increased inequality may, however, provide a reason to abstain from human enhancement.

Human enhancement and social polarization

The already existing gap between rich and poor may be further exacerbated both within and between countries if the technology improves and our knowledge about genetics extends sufficiently to enhance traits such as intelligence and physical fitness. Wealthy people already have an economic advantage, and the concern is that allowing germline editing for enhancement purposes will give them a genetic advantage as well. If so, will those who cannot afford genetic enhancement be left worse off than they would have been if no one had used the technology to enhance their children's genetic characteristics? Can it be said that 'unenhanced' people are harmed by this? Consider the following case:

Case 5: Social polarization

(Note that this case is highly imaginary. I do not suggest – nor do I believe – that this will actually happen).

Imagine that ten years from now, the legislation on human germline editing changes to allow genetic enhancement. Scientific progress has improved the technology and extended our knowledge about genotype-phenotype correlations, and it is now possible to change virtually any genetic characteristic. Genetic intervention to enhance human characteristics is allowed as long as it is expected to increase the child's well-being in one way or another. The technology is expensive and thus only accessible to wealthy, privileged people, meaning that it will only be available for those who already have an economic advantage. Suppose that all, or at least the majority, of those who can afford the technology uses it to genetically manipulate their prospective children in order to give them certain advantageous genetic characteristics. As a result, the wealthy people will have both an economic advantage and a 'genetic advantage.' Those who cannot afford the technology will be left even further behind with their 'unfavorable genes'. The gap between the rich and poor will increase as wealthy people become more superior for every generation.

The thought of adding even more inequality to the already existing inequality is indeed unsettling. If the enhancements are ‘positional goods’ that give a competitive advantage, for example, in the job market, the disadvantage of not having the enhancement will be even bigger. The ‘unenhanced’ may, for instance, have a harder time getting a good job and may thus never get enough money to afford the enhancement technology. They may also experience discrimination and prejudices, aggravating the inequality even further.

A potential way to avoid increasing inequality is to ensure that everyone gets access to the enhancement technology (this is a rather utopian thought but suppose that it is possible). Everyone will then have the same possibility to enhance their children, and no one will be ‘left behind’ with ‘disadvantageous’ genes. The problem is that the advantage of being enhanced will decrease as more people have the advantage, and the technology may, in that sense, be self-defeating. Glover (2006) explained this by comparing it with the advantage of a university degree. A master’s degree may give a competitive advantage in getting a job, and that advantage may be the reason why some people value the degree. The greater the advantage is, the more people are likely to apply to universities, and the universities may then expand in response to the increased demand. As more people get a master’s degree, the advantage of having one will decrease. It may therefore be necessary to do a Ph.D. in order to keep the advantage in the job market. The circle will then repeat itself, and we have “collectively walked into a trap” (Glover,

2006). No one has the advantage if everyone has the advantage; or, as Fred Hirsch said: "if everyone stands on tiptoe, no one sees better" (Hirsch, 1977 p. 5).

Genetic enhancements may, however, also be 'absolute goods', meaning that they are valued irrespective of the advantage they may give. These enhancements will be beneficial even if the competitive advantage is nullified. For instance, good health would be beneficial regardless of how many it is that have good health. Also, the vast majority of phenotypes are determined by more than just genetics, and the enhancement is unlikely to have an identical effect in every person. The enhanced traits will most likely be 'gradual', meaning that the enhancement will not be the same in every enhanced person. For instance, those with enhanced intelligence will not have the same IQ.

However, equal distribution of gene technology seems rather unrealistic (especially for human enhancement). Even so, can something be banned simply because not all can benefit, as with the 'dog-in-the-manger' version of egalitarianism? Not everyone with poor eyesight can afford glasses, but that does not mean that no one with poor eyesight can use glasses. Will the people who do not have access to gene technology be harmed by the fact that others are genetically engineered? 'Unenhanced' people may experience psychosocial harms from prejudices and discrimination, and the genetic enhancement may thus contribute to causing psychosocial harm. However, it has been argued that it is not the human enhancement itself that will cause harm to others. As stated by David Resnik (1994): "Rather than focus on these contributing factors, we should focus on the underlying problem, i.e., people's attitudes and stereotypes. This underlying problem is best solved through education, not by suppressing technological developments which may contribute to it" (p. 32).

If people who cannot afford genetic enhancement are not harmed by the genetic enhancement itself but by social stigmas and prejudices, why is genetic inequality considered worse than economic inequality? One reason is that genetic inequality is particularly hard to reduce (Glover, 2006). Once you have developed past the embryonic stage, it is practically impossible to change your genetic makeup. Your economic status, on the other hand, can change. It is not written in stone that you will be poor your entire life just because you are born poor, and it is definitely not written in stone that you will be rich forever just because you are born rich. The economy may change, and actions can be taken to reduce economic inequality. Genetic inequality will be much harder to reduce and will most likely be passed down to subsequent generations.

Enhanced rat race

The development and improvement of technology are a constant and often rapid progress, and biotechnology is not an exception. Robert Sparrow has suggested that because of the rapid development of enhancement technology, "each cohort of enhanced individuals will find itself in danger of being completely outdated by the next competition of important social goods" (Sparrow, 2015 p. 231). This may, according to Sparrow, cause an 'enhanced rat race' where certain enhanced genetic traits (and thereby the enhanced person) may be obsolete already by the time of birth, or at least in early childhood (Sparrow, 2015; Sparrow, 2019).

The enhanced rat race may have a considerable impact on society and on the individuals if it is to occur. As soon as we begin to genetically enhance human beings, the genomes of those who are not enhanced will become obsolete, and "every human being will eventually discover her- or himself to be 'yesterday's child" (Sparrow, 2019 p. 13). Enhanced individuals will start 'on top' with the advantage of having the 'newest' and 'best' enhancements, but the advantage will decrease for every generation that is born with even newer and better enhancements. The individual may experience exclusion from more and more aspects of the social and economic life as his/her enhancement becomes more obsolete for every new generation.

However, as pointed out by Hofmann (2019), the problem is not that the enhancement will be obsolete but that we will change our values. Also, Sparrow's suggestion that enhancements will become obsolete seems unlikely from a biotechnological point of view. The enhancement is, after all, not the technology itself but our altered genetic makeup. The development and improvement of the technology will thus not be sufficient to improve the enhancement; improvement of the possible phenotypes is also necessary. Although advances in genetics may make it possible to 'artificially' create better phenotypes, it is more likely that genetic enhancement will be based on selecting a preferred phenotype from the already existing phenotypes rather than *creating* a better phenotype. Genetic enhancement can, in that sense, be seen as 'enhanced evolution' where each generation will have 'a larger collection' of preferred phenotypes. Given that the human generation time is relatively long, it seems unlikely that enhanced human beings will become obsolete – at least not in the rapidity proposed by Sparrow.

Equality of opportunity

Germline editing has also been suggested to provide a potential method to diminish inequality. People have different opportunities not only because of social inequalities but because of the unequal distribution of genetic endowments. Some are born with advantageous genetics that greatly improves their chance of success, whereas others are born with adverse genetic disease

that limits their opportunities and reduces their chance of creating a life they want. Genetic disadvantages are usually seen as a natural inequality that no one can control. Most people agree that genetic disadvantage ought to be compensated for by, for instance, treating genetic disease in order to reduce the opportunity-limiting effect it may have. Genetic disadvantages have, however, been outside the scope of human control and have therefore been seen as a matter of bad luck rather than as an injustice. Nevertheless, as the development of gene technology has made it possible to intervene in the genetic lottery, it has been proposed that genetic disadvantage should be seen as a matter of injustice (Buchanan et al., 2000)

> If precise and safe control over the distribution of natural assets becomes feasible, then those who believe that justice is concerned with the effects of natural assets on individuals' life prospects will no longer be able to assume that justice requires only that we compensate for bad luck in the natural lottery by intervening in the social lottery, rather than by attacking natural inequalities directly (Buchanan et al., 2000)

The 'level playing field' concept of equality of opportunity holds that people's opportunities should not be determined by factors they cannot control. This will often require efforts to counteract or compensate for unequally distributed assets in order to eliminate (or at least reduce) the opportunity-limiting effect. Instead of just compensating for the inequality of opportunities brought about by genetic disease and disability, we can now remove the cause directly. Thus, germline editing can provide a remedy to level the playing field.

PERSONAL IDENTITY AND AUTONOMY

Many have expressed concerns about the psychological harm germline editing may have on the individual. Habermas has suggested that to change the uncontrollability of human fertilization – the 'unforeseeable' combination of two chromosomes – into something we can control will interfere with the individual's ability to be oneself (Habermas, 2003). Others have suggested that to genetically manipulate an individual is to coerce its own will on another individual, and the genetically engineered individual is thus be deprived of its autonomy and freedom to choose its own destiny.

> For as soon as adults treat the desirable genetic traits of their descendants as a product they can shape according to a design of their own liking, they are exercising a kind of control over their genetically manipulated offspring that intervenes in the

> somatic bases of another person's spontaneous relation-to-self and ethical freedom. (Habermas, 2003 p. 13).

Arguments about the child's right to freedom of choice and an open future stand strong in the germline editing debate and are often seen as reasons *not* to allow germline editing. However, germline editing can also be seen as a way to ensure the individual's capability is to create its own future by removing the limitations that often (although not always) come with disease and disability.

Personal identity

DNA can be thought of as 'the blueprint of life' because it provides the instructions an organism need to develop, survive, and reproduce, as well as a 'recipe' for a wide range of genetic characteristics. DNA can, in that sense, be said to constitute the very foundation of what makes a particular human being that exact human being. The idea of DNA as what makes you '*you*' give rise to worries regarding how alterations in DNA may change the individual's personal identity and interfere with the individual's ability to create their own future.

> What is worrying about so-called "enhancement technologies" may not be the prospect of improvement but the more basic fact of altering oneself, of changing capacities and characteristics fundamental to one's identity (Elliott, 1999).

We are a product of our genes in the way that our genes provide the recipe for developing our characteristics. But are we a product of our genes in the sense that our whole personal identity is programmed in our genes? No, we are not. Our genes provide the range of possible phenotypic characteristics, but which particular phenotypes that will be expressed are highly influenced by environmental factors. Thus, personal identity and the creation of the *self* are influenced by both biological and environmental factors throughout the entire life. Environmental influence from parents, school, interpersonal relationships, etc., are constantly shaping our identity. The difference is that the child can, at least to some extent, choose to chance (or more correctly, choose whether or not to act in accordance with) this external influence later in life. Changes in the genetic makeup are, in contrast, irreversible, and the child will not be able to reverse these changes later in life. However, as argued by David Resnik (1994), the majority of genes are not deterministic, and the shaping of who we are depends on more than just our genetic constitution.

> As long as we are not completely determined by our genetic programming, knowing that someone designed that programming should not threaten our conceptions of ourselves as independent people. As long as we think of ourselves as more than just our genes – and most people do – this knowledge should not threaten us (Resnik, 1994)

Also, analogously to the arguments that germline editing cannot be seen as therapy[20] because the person does not yet exist and neither does the disease, one can argue that germline editing cannot change the person's identity because the embryo does not have an identity that can be changed. The embryo may develop into a different child than it would have without the genetic intervention, but can the germline-edited individual claim that he/she has been harmed because he/she would have been a different person without the genetic intervention? If that is the case, that the person's identity would have been a different person were it not for the germline editing, the germline edited individual would not have been born otherwise – it would have been another person. Thus, the germline edited individual cannot complain that he/she was harmed by the genetic intervention because that exact individual would not be that individual if the gene-editing had not been done. The only reason why the child then can complain is if the child's life is not worth living and that he/she would have been better off he/she had not been born.

Autonomy

Respect for autonomy is one of the key principles in biomedical ethics. To be autonomous means, in general terms, to be one's own person and to act in accordance with its own choices, values, and desires. Personal autonomy at a minimum level "encompasses self-rule that is free from both controlling interference by others and limitations that prevent meaningful choice, such as inadequate understanding" (Beauchamp & Childress, 2001 p. 101).

Autonomy is relevant to the germline editing debate in three main areas: the (future) child's inability to give consent, the impact on the child's freedom to choose its own future (the right to an open future), and the patents right to make free choices (reproductive autonomy). The parents' wishes can sometimes be in conflict with the child's best interest, and the balance between reproductive autonomy and the child's future autonomy can be challenging (discussed in Chapter 6). The inability to obtain consent from the child aggravates the problem.

[20] Note that germline editing to correct disease is seen as therapy in this thesis. This is briefly discussed in *Chapter 4: Drawing the line between therapy and human enhancement*. For further elaboration on this subject, see Glannon, Walter. (2003). Genetic intervention and personal identity. In Brenda Almond & Michael Parker (eds) *Ethical issues in the new genetics: are genes us?* (chapter 7). England: Ashgate.

Consent

One of the problems with germline editing is the fact that the person that will have their germline edited cannot give consent because that person does not yet exist. Germline editing can thus be said to violate the child's autonomy, and it has been argued that research on germline editing should be not be permitted (Smolenski, 2015). However, children cannot consent to anything regarding their birth; they can neither consent to nor decide whether to be conceived, what circumstances they are born into, their genetic constitution, and so on (Ranisch, 2017).

One can argue that informed consent is not required if the genetic intervention is for therapeutic reasons in the same way as medical treatment of unconscious persons does not require consent. The genetically engineered person may complain that he or she was harmed and that he/she could have been different if the genetic engineering had not taken place, but a diseased person might also complain that he/she was harmed by the failure to prevent the disability. Some may argue that there is an important distinction between 'causing harm' and 'failing to prevent harm' in the same way that it is a contrast between 'taking a life' and 'failing to save a life'. The outcome is the same – the person will still be dead, or the diseased will still have the disease – but in the case of 'causing harm' or 'taking a life', there will be a justified reproach against the person causing harm or taking the life. If the genetic disease is fatal, it can also be argued that complaints that the intervention violated the child's autonomy may seem nonsensical because the subject would not be alive if the intervention had not taken place. Even so, the germline edited individual can complain that his/her life is not worth living and that the parents harmed him/her by saving him/her life. But then again, can anyone really blame their parents for being alive? As Glover (2006) said: "how can it be that we owe it to the child to prevent his or her life?".

The inability to obtain informed consent becomes more problematic in the case of human enhancement, mainly because it is impossible to know what the child will desire and thus which traits the child will value (discussed more in Chapter 6). Many advocates for human enhancement do, however, claim that it is permissible and maybe even obligated as long as the intervention does not impede the child's right to an open future.

The child's right to an open future

The principle of a child's right to an open future was first characterized by John Feinberg and holds, in general terms, that children should have as many skills and capacities as possible (or at least within a reasonable range) to create and choose their own future when they become

autonomous adults (Feinberg, 1992). The child's right to an open future is a so-called 'rights in trust', which means that it is a future right that should be saved for the child until it becomes old enough to exercise it. Parents should give their child as much input as possible in order to provide the child as many opportunities as possible, or at least the same opportunities as other children, as well as protect the child from making any choices that will limit its options later in life (Feinberg, 1992).

A child's right to an open future is commonly appealed to on both sides of the germline editing debate. Some have suggested that germline editing will limit the child of its freedom of choice and thus interfere with its chance to create its own future (Habermas, 2003), whereas others have suggested that it will promote an open future by broadening the range of opportunities through genetic enhancements (Juth, 2011). However, there seems to be a general agreement among both sides that germline editing to remove disease is likely to promote an open future and that those genetic enhancements that limit the range of future opportunities should be avoided (Malmqvist, 2007).

Disease or disability can severely limit the range of future opportunities, and one can therefore argue that it should be removed in order to give the child more freedom to create its own future. Buchanan et al. (2000) argued that to claim that germline editing violates the child's right to autonomy is implausible because

> genetic interventions might in fact be less threatening to individual autonomy and privacy and more likely to succeed at removing barriers to opportunity than the kinds of large-scale changes in family life needed to counteract the opportunity-limiting effects of disadvantages in family culture and early childhood experiences (Buchanan et al., 2000, p. 78)

Germline editing for enhancement purposes can also be seen as a way to promote an open future by giving the child capacities that broaden the range of opportunities. The genetic enhancement may also give the child better abilities to realize its dreams and desires (Juth, 2005; Juth, 2011). For instance, enhancement of cognitive abilities may help the child to realize its dream to become a scientist, and enhancement of physical strength may help a child realize its dream to become a professional athlete. The problem is if the enhanced cognitive ability is at the expense of physical strength, or if the enhanced physical strength is at the expense of cognitive abilities because there is no way of knowing what the future child would value the most.

Some objections to human enhancement are based on a concern that parents may become too 'goal-oriented' and create a child according to a specific 'goal' or desire they have. In order to create a child with specific characteristics, the parents may choose genetic traits that are beneficial under specific circumstances or for certain life plans but often at the expense of other goods (Fox, 2007). The risk is that the parents may choose genetic characteristics that are so 'narrow' that it leaves no room for the child's own self-creation. The child will thus be 'committed' to a specific life project it did not itself choose and will have no choice but to pursue the parent's goals and desires rather than its own. The child may also suffer psychological harm from bearing the burden of having to live up to the expectations of its 'design' (Kass, 2003), and the child will, according to Habermas (2003), be unable to see itself as the 'undivided author of its own life" (p. 63).

> Eugenic programming of desirable traits and dispositions, however, give rise to moral misgivings as soon as it commits the person concerned to a specific life-project or, in any case, puts specific restrictions on his freedom to choose a life of his own (Habermas, 2003 p. 61)

It can be argued that since our values and desires are likely to be highly influenced by our characteristics and capacities, our values and desires would not be *our own* (self-governed) if our capacities are brought onto us by another person through genetic intervention and acting on these desires would thus not be autonomous (Juth, 2011). However, our values desires are also highly influenced by the environment we grow up in and are thus never fully controlled by ourselves. To claim that it reduces autonomy to act on *non*-self-governed desires for the reason that 'the person acting is not self-determined and is therefore not autonomous' is problematic because it disregards the person's own decision to act (Juth, 2011). Hence, autonomy is contingent on the person's *capacity to decide for oneself* whether to act on the desire rather than the *origin of the desire.*

Reproductive autonomy

It is widely agreed upon that people should have the right to make their own decisions regarding reproduction. Emerging reproductive technologies are often seen as a way to increase reproductive autonomy by expanding the scope of reproductive choices. Germline editing can be especially important to ensure reproductive autonomy in cases where preimplantation

genetic testing is unsuccessful[21] (Cavaliere, 2018). There are, however, some disagreements to whether reproductive autonomy should include the freedom to choose the child's genetic characteristics. This is discussed more in *Chapter 6: Choices and obligations when creating a child*.

The selfish-argument

It has been suggested that the preference for a healthy child without diseases or disabilities is based on a selfish desire that deprives the child of unconditional acceptance; that it is grounded in the desire to avoid the additional difficulties and challenges with raising a child with special needs (Glover, 2006). All children are entitled to unconditional love and acceptance, and this love and acceptance should not be contingent on whether the child is able-bodied or disabled, healthy or ill. Rather than attempting to remove any potential obstacle, one should instead ensure that the child receives the unconditional love and acceptance all children are entitled to.

However, the 'selfish-argument' is problematic in at least two ways. First and foremost, it creates a false dilemma between the preference of a child without a disability and the child's need for unconditional acceptance. To want your child to have a life without disability or disease is not equivalent to not accepting your child if your child happens to be disabled. Secondly, the argument falsely assumes that the parent's preference for a child without disability is grounded in a belief that having a child without disability is easier than having a child with a disability and that a child with a disability is an inconvenience that will make their life more difficult.

Raising a child is not an easy task free from difficulties and challenges. The journey of parenting has no definite, planned-out route, but there is no denying that it is accompanied by numerous worries about their child's well-being. Parents strive to ensure that all aspects of their children's lives are as good as possible and are often worried that they fail in accomplishing a safe and successful life for their child, that their child will encounter difficulties of any kind, or that their child will be exposed to harm and pain. These worries do not magically arrive at birth. The prospective parents will strive to give their child the best life possible, and worries about their child's well-being will start the very second the pregnancy is confirmed, sometimes even earlier.

A variety of choices are being made by prospective parents to reduce the possibility of their child being born with a disease or disability. The prospective parents are likely to

[21] See *Chapter 3: Germline editing with CRISPR/Cas9*

purposely abstain from things that can harm the child and make sure that the mother gets adequate nutrition to ensure normal fetal development. They will start childproofing their home to ensure the child's safety and invest in expensive equipment to ensure the safety even further. None of these actions can be said to be selfish. Not performing these actions are, in contrast, often seen as irresponsible and reckless. No questions are asked when a pregnant woman avoids alcohol, cigarettes, and other drugs for the sake of not harming her baby. Many will even argue that using such substances is a form of child abuse because it puts the developing child at substantial risk of numerous health problems. No one would claim that the child was harmed by the mother's decision to quit smoking, even though the child might have turned out differently if the mother had continued smoking during pregnancy.

Just as actions to ensure the child's safety does not mean that the child will no longer be loved and accepted if it gets harmed, actions to prevent disease or disability does not mean that the child will not be loved and accepted if it is born with a disease or a disability. In some cases, the disability might enrich the family, and the disabled person and his/her family may cope brilliantly. But a disability might just as well be devastating both for the affected person and for the relatives. Take, for instance, Tay Sachs disease – an autosomal recessive disease often resulting in death by the age of 4. Imagine a couple who want to have a child, but they are both carriers of Tay Sachs. Can they be blamed for not wanting their child to inherit Tay Sachs disease? Are the parents selfish if they are unable to cope with the fact that their child will most likely die at a very young age? Even in cases of non-fatal genetic disease, its manifestations may have tremendous negative impacts on the individual's quality of life. Is it immoral of parents to want their child to have the best possible quality of life? I think not.

Even if the genetic disease does not necessarily cause pain and suffering, it may cause special needs and profound difficulties that will affect every aspect of the parents' future life. Is it wrong of parents not to want that? Parenthood is, as Thomas Murray said, "a region where the boundary between self-interest and concern for the child gets hopelessly blurred" (Murray, 1996). The wish for a child without disease or disability is most likely to be grounded in both self-interest and concern for the child. But even if it was grounded solely on self-interest, it is dubious whether it can be said to be morally wrong of parents to intervene in their child's genetic makeup in order to remove the disease. It may even be that they, self-interest aside, have an obligation to do so.

CONCLUSION

The potential consequences of germline editing raise many ethical issues, but the bottom line is that most of these are not exclusive to germline editing. Similar ethical issues can be seen in other areas of medical research and technology, as well as other actions carried out by parents to give their children the best options in life. Although some of the potential consequences can have considerable negative effects for the individual as well as for society as a whole, the consequences are primarily related to human enhancement and do not give justifiable cause to not proceed with therapeutic germline editing. Besides, the genetics behind most 'enhancement traits' (such as intelligence, physical strength, etc.) are not yet fully understood due to complex inheritance patterns involving several genes. Germline editing is thus mainly limited to changing monogenic traits due to technological limitations and shortcomings in our understanding of genotype-phenotype correlations. Although this might change, it seems rather implausible to prohibit a life-saving technology based on the fact that the technology *may* someday in the distant future be used for purposes not yet possible.

CHAPTER 6

CHOICES AND OBLIGATIONS WHEN CREATING A CHILD

The 'genetic lottery' has never been a fair[22] game. People are born with different genetic characteristics and thus also different opportunities and chances. Whereas some people are given genes that increase their chances of a long and healthy life, others are handed genes that cause disease and early death. Whether you are given 'good' genes or 'bad' genes is based on pure luck. The development of CRISPR gene technology has, however, changed the rules. Genetic intervention can rescue people from genetic disadvantage[23] and could, in principle, promote a level playing field. There is a general consensus that severe medical conditions should be treated if possible and many go to extreme lengths in an attempt to treat, or at least manage, severe disease after the child is born. But would it not be a better option to remove the disease before it could do any harm and simultaneously prevent the disease from being passed down to subsequent generations? To remove the cause of the harm directly, rather than to compensate for harm in every generation, is perhaps a substantially more viable option.

This gives rise to numerous questions about responsibility and obligations regarding procreation. Who is responsible for genetic disease? Can parents be blamed for harming their child if they 'choose not to prevent' their child from being affected by a genetic disease? Will this create an unbearable pressure on prospective parents? Genetic disease or disadvantages can be said to be caused either by avoidable actions (e.g., drinking alcohol during pregnancy) or failure to prevent disease/disability (e.g., reject gene editing). Whereas the former gives obvious candidates for injustice, failure to prevent genetic disease or disability is usually viewed as

[22] There are some disagreements to whether the genetic lottery can be said to be unfair because, like all other lotteries, it is completely arbitrary and is therefore more correctly seen as a matter of good or bad luck. The increasing control over the genetic lottery may however change genetic disadvantage from a matter of 'brute luck' to a matter of unfairness. See Hauskeller, Michael. (2016). Levelling the Playing Field. In Steve Clarke, Julian Savulescu, C. A. Coady, Alberto Giubilini & Sagar Sanyal (eds) *The ethics of human enhancement: understanding the debate* (chapter 14). Oxford University Press.

[23] Certain genetic diseases and disadvantages are (and will probably be for a very long time) still incidental because: (1) gene editing with CRISPR/Cas is so far limited to monogenic diseases/traits due to technological limitations and insufficient knowledge about genotype-phenotype correlation, and (2) disease-causing mutations can occur spontaneously. Germline editing require targeted editing in early-stage embryos and is therefore primarily limited to inherited disease-causing mutations.

natural or inevitable. Nonetheless, the 'failure to prevent' can be related to someone's responsibility and may therefore be seen as an injustice (Buchanan et al., 2000; Glover, 2006).

Given that CRISPR technology provides a possible way to rescue people from severe genetic diseases, it has been suggested that it is a prima facie obligation to do so. Buchanan et al. (2000) argue that where genetic intervention to correct a child's disability is possible, it should be seen as part of what we owe to the child (Buchanan et al., 2000). A shift of focus from the impact of germline editing to the impact of genetic diseases may even opt for a more sensible and prudent pathway in the establishment of ethical guidelines. The impact of disease and disability is, to a certain degree, possible to assess by interviews and Quality of life measurements of affected individuals. Although the concept of disease is debated, it is generally agreed upon that disease can have substantial negative effects on all aspects of life. However, the experience of a particular condition and the individual's ability to cope with it is highly subjective and dependent on more factors than just the disease itself. Whereas a functional impairment can be devastating for some people, it might enrichen other people's life with qualities of character they otherwise would not have. In this respect, an inevitable question arises regarding genetic engineering: can anyone without personal experience with a particular condition be qualified to decide whether or not this particular condition is a disability that should be removed?

PURSUING THE GOOD LIFE

The aim of germline editing – both for therapeutic and enhancement purposes – can be said to be 'the good life'. But what is a good life? The good life is perhaps one of those few things all want, but no one really knows what is. Some people spend their whole life pursuing what they think is a good life, only to find out that it was not what they wanted after all. Others have a clear conception of what constitutes a good life, but their version of a good life may be in stark contrast to what others see as a good life. So how can parents possibly know what a good life for their future child will be? Are there some things in life that are good for all?

What is a good life?

The good life is often seen in terms of well-being, which describes what is good *for* someone (Crisp, 2017). Well-being can be understood based on different theories, e.g., hedonism, desire-fulfillment, and objective list theories (Griffin, 1989; Parfit, 1986). The hedonistic view holds that well-being is the greatest balance of pleasure over pain, and what matters is the quality of

our experience of pleasure (Crisp, 2017). But a good life involves more than just enjoyment of pleasure, and life can still be good even if it involves pain.

Desire-fulfillment theories see well-being in terms of satisfaction of desire. The desire can be seen in terms of a *present desire*, in which well-being is the degree to which current desire is fulfilled, but this version is problematic because what you desire is not always what is good in the long run. To act on temporary desires may give a brief sensation of happiness, but it may interfere with the person's overall well-being. The desire-fulfillment theory is best seen in terms of *comprehensive desire*, which holds that well-being is the level of desire-satisfaction in life as a whole. Although satisfaction of desire may be important for a good life, our desires are subjective and may change throughout our life course. Desire-fulfillment theories are therefore not sufficient to fully understand what constitutes a good life for all.

The third version of well-being, objective list theories, are theories that list the things that are good for people. Different theories have different things on the list, but the list can, for example, include knowledge, friendship, dignity, etc. (Crisp, 2017). One problem with objective list theories is that they disregard how the person feels about their own life. The items on the list are assumed to be good for people even when they do not want them. 'All-purpose goods' are traits that are valuable regardless of which kind of life a person chooses to live and are thus valuable on all plausible conceptions of well-being (Buchanan et al., 2000; Savulescu et al., 2011). These traits include memory, self-discipline, patience, empathy, a sense of humor, optimism, etc. (Savulescu et al., 2011).

Hence, well-being can be seen in different ways, but none of the abovementioned versions give a satisfying definition of what constitutes a good life. Several factors must be taken into account in deciding whether a particular person has a good life, but even what factors are important may differ. The attempt to define what constitutes a good life seems to create a paradox where it must be answered objectively to regard all people, but a good life cannot be defined without including the subjective conception of a good life. Perhaps the best way to understand what constitutes a good life is to combine different well-being theories, but that would probably be both too narrow and too broad to assess a universal model of a good life that is a good life for everyone.

Germline editing to aim for the good life may be to shoot for the sky. But the *good* life may not be that important as long as the germline editing results in a *better* life. But how can we know what 'a better life' is? Is species-typical normal functioning always better than abnormal function? Take deafness, for instance, which is commonly thought of as a disability, although many people who are deaf do not consider their deafness as a disability. How can we

know for sure that it is better to be able to hear than to be deaf? John Stuart Mill proposed the idea of higher and lower pleasures where "some kinds of pleasure are more desirable and more valuable than others", and people's happiness can be assessed by including an estimate of the quality of their pleasure (Mill, 2009). Given the choice between two pleasures (or, in this case, genetic 'conditions'), the most desirable pleasure is the pleasure preferred by all or most of those who have experienced both. However, it is extremely unusual to experience both "states" of a genetic condition – you are either affected, or you are not. Nonetheless, the harm caused by some genetic diseases can be so severe that it would be nonsensical to claim that it is better to be born with the genetic condition than to be born without.

In addition to – or as an alternative to – Mill's idea of higher and lower pleasures, one can gain valuable information about how disease impacts well-being by studying Quality of life measures. Quality of life (QoL) is defined as "an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns" (World Health Organization, 2012). QoL is a measure of a person's overall well-being based on all major aspects of a person's life. Numerous scales have been developed to measure QoL under different conditions and circumstances. Generic scales can be used to assess any health condition and are useful to study differences between groups or populations, whereas disease-specific scales are often more specified and are used to analyze specific conditions (Cohen & Biesecker, 2010).

Although QoL is not a measure of health per se, there is no doubt that health has a significant impact on QoL. Several disease-specific QoL studies have shown that genetic disease can have a significant negative effect on QoL. The negative effect is related to more than physical health and functioning. Psychosocial factors such as psychological well-being, coping strategies, and family functioning are indicated to be just as important as the genetic condition (Cohen & Biesecker, 2010).

CASE 2: HUNTINGTON'S DISEASE

Quality of life (QoL) assessment show that Huntington's disease has a severe negative effect on physical and psychosocial well-being, with a particularly high impairment in the "work" and "alertness behavior" domains (Helder et al., 2001). Other studies have shown that Huntington's disease has a severe impact on family functioning (Vamos et al., 2007). Thus, family members' QoL may also be negatively affected.

WHICH TYPE OF CHILDREN CAN WE CREATE?

Emerging reproductive technologies have the potential to increase the parents' possibilities to control what kind of child they have and put pressure on the difficult balance between reproductive autonomy and the child's future autonomy. It is widely accepted that decisions regarding *if* and *when* to have a child should be taken by the person themselves. To what extent prospective parents should have control over *what* child they will have, on the other hand, are significantly more disputed. Parents make decisions on behalf of the child every day – both before and after birth – that will affect the child in various degrees. Decisions about what the child eats, what school the child should go to, what activities to participate in, etc., can have a major impact on who the child grows up to be, but these decisions are nonetheless made without knowing what the child's own wishes and desires. In the same way as these decisions are considered permissible, some might consider germline modifications as just another kind of decision parents make daily for their children. There is, however, a significant difference in the degree to which the decision can impact every aspect of the child's future life.

Nonetheless, some may argue that parents should be allowed to create any type of child they want. The libertarian approach is based on strong procreative liberty and holds that it is morally permissible for parents to create any kind of offspring they want, regardless of the offspring's chance to pursue a good life (Liao, 2019). One problem with this approach is the fact that some parents may want nonbeneficial interventions for their children. It will, for instance, be permissible to create children with diseases such as Tay Sachs and Huntington's (although it is highly unlikely that any parent would want that). It is questionable whether anyone supports this approach. James Watson, who discovered the structure of DNA together with Francis Crick, said the following in an article in The Guardian in 2003:

> I am against society imposing rules on individuals for how they want to use genetic knowledge. Just let people decide what they want to do. Anything - a short child, a tall child, an aggressive child ... I'm for using genetics at the level of the individual… It is best to let people try and do what they think is best. I wouldn't want someone else to tell me what to do - as long as you are not hurting someone else (Radford, 2003)

Ronald Green (2007) also defends the strong procreative liberty and claims that parents are allowed to "mold their child's nature in directions shaped by the parent's own hopes for their child, including the use of gene modification" (p. 127). However, Green points out that

the intervention must be within the limit of what can be understood as in the child's best interest (Green, 2007). Although the parents' desires will be coherent with the child's best interest in most cases, the libertarian approach is not sufficient for the regulation of germline editing. A justifiable approach needs to make sure that the child has – as a bare minimum – a life that is worth living.

> Parental freedom should be constrained by the interest of the child in having a good life. Where a particular child can be saved from disability by genetic intervention, this is something parents owe to the child unless there are strong countervailing reasons (Glover, 2006, p. 62).

What we owe to the child

Genetic diseases can have a major impact on every aspect of a child's life. Severe pain, long-term hospitalizations, impaired ability to flourish, shortened life expectancy, etc., are only some of the consequences of adverse disease. Tay Sachs disease, for example, causes years of suffering and affected individuals rarely live longer than five years. Another example is Lesch-Nyhan syndrome, a monogenic disease caused by mutations in the *HPRT1* gene that encodes the enzyme hypoxanthine-guanine phosphoribosyltransferase (HPRT) (Jinnah et al., 2000; Jinnah et al., 2004). The deficiency of HGPRT enzyme causes accumulation of uric acid in all body fluids, and symptoms include mental retardation, compulsive self-harm, dystonia, chorea, kidney stones, spasticity, intellectual disability, hyperuricemia, kidney failure, and megaloblastic anemia (Jinnah et al., 2006; Lesch & Nyhan, 1964; Torres & Puig, 2007). The lack of a cure or efficient treatment for most genetic diseases exacerbates the suffering. To the extent that genetic disease can be prevented, it is a prima facie obligation to do so irrespectively of what the cause is. As Buchanan et al. (2000) argued: "the question is not whether or in what sense a disease is genetic, but whether or not there is an intervention (genetic or otherwise) that can cure or prevent it" (p. 16).

Parents are responsible for making medical decisions on behalf of their children, and they have the authority to refuse or stop medical treatment. But parents also have an obligation to ensure that their children receive appropriate medical treatment when necessary. Children's right to appropriate health care is so fundamental that many countries have legislation that permits the state to take temporary guardianship of the child if the parents disapprove of life-saving treatment for reasons such as religion, for instance, if Jehovah's witnesses refuse to approve blood-transfusion. Can this apply if parents refuse to approve genetic interventions that will prevent adverse genetic disease? Or in other words, do parents harm the child if they refuse

preventative interventions? It is, according to Steinbock and McClamrock (1994), "possible for a child to be harmed by negligence that occurs prior to that child's conception, when no being… exists" (p. 15). However, the conception must occur via in-vitro fertilization (IVF) for germline editing to be possible, and since genetic disease can arise spontaneously, 'coercive' prevention of genetic disease would require every conception to occur via IVF. This would not only violate reproductive autonomy, but it would bring us back to the 'old' eugenics. One can, however, argue that parents have a prima facie obligation to prevent genetic disease whenever possible.

It can be argued that it is justifiable to refrain from germline editing to correct a genetic disease as long as the child is expected to have a life that is worth living. But how terrible can we accept a life to be before it is no longer worth living? The' zero-line view' of a life worth living holds that it is permissible to have a child as long as we expect the child's quality of life to be slightly better than 'very terrible'. But a life barely worth living is far from a good life. Is it permissible to create a child that is expected to have a life that is barely worth living when we have a technology that can drastically reduce the suffering? It has been argued that a quality of life that is just above the very terrible level is not good enough. Frances Kamm suggested that it is wrong to create a child with avoidable defects and that the 'zero-line' instead should be placed at normality (Kamm, 1992). A similar argument has been proposed by Bonnie Steinbock and Ron McClamrock, who said that it is wrong to bring a child into the world unless it has a "decent chance at a good life" (Steinbock & McClamrock, 1994, p. 17).

> Anyone willing to subject a child to a miserable life when this could be avoided would seem to fail to live up to a minimal ideal of parenting (Steinbock & McClamrock, 1994, p. 18)

S. Matthew Liao (2019) has suggested that it in some cases may be morally impermissible not to correct harmful genes that cause defects in fundamental capacities. Fundamental capacities are capacities that human beings need in order to pursue basic activities, such as "the capacity to think, to be motivated by facts, to know, to choose an act freely (liberty), to appreciate the worth of something, to develop interpersonal relationships, and to have control of the direction of one's life (autonomy)" (Liao, 2019, p. 100). Human beings have a right to have the fundamental conditions and capacities required to pursue a good life, and it is a duty to ensure that every human being has these fundamental capacities as long as it is not too demanding (Liao, 2019). These capacities can, however, be difficult to define, and many of them are likely to be more contingent on environmental factors than on the genetic constitution.

Nonetheless, to the extent that it is possible to prevent the child from lacking any fundamental capacity, it should be seen as something we owe the child. This is supported by both the moral obligation to prevent harm and the parental obligation to ensure that the child is provided appropriate health care when needed. To force parents into genetic intervention in order to prevent harm would, however, violate reproductive autonomy, but parents should have the possibility to choose to prevent their child from having a genetic disease whenever it is possible to do so.

Permissibility of human enhancement

Despite the many ethical concerns regarding the possibility to enhance the characteristics of human beings, it can also be highly beneficial to enhance certain human characteristics above what is seen as 'normal'. The prospect of human enhancement has gained support from numerous commentators claiming that parents have should have the right to choose their child's genetic characteristics (Green, 2007). It has even been suggested that it is a parental obligation to ensure that their children have the best chance to the best life (Savulescu, 2001; Savulescu & Kahane, 2009)

> If prospective parents have moral reasons to care about the potential for well-being of their future children, then it would seem that they should also have reason to *aim* to have children who are more advantaged rather than leave this to chance or nature (Savulescu & Kahane, 2009, p. 276)

As discussed in the previous sections, there are some disagreements as to how disease and disability differ from typical 'enhancement traits'. Disability is often seen as an obstacle to human flourishing because it puts limitations on the disabled person's life – and since the ability to flourish is generally considered a necessity for a good life, these obstacles should be removed in order to give the child the best chance, or at least a 'normal' chance to flourish (Glover, 2006). But disability is not the only thing that can impair the ability to flourish; traits such as shyness and laziness can also have a limiting effect on flourishing. If it is accepted to remove disease and disability in order to give an individual the ability to flourish, it may be other traits that should be removed as well. What makes the elimination of *medical* obstacles permissible and perhaps even obligated while human enhancement is seen as ethically unacceptable? An easy answer can be that removal of disease and disability restores normality, but this can relatively easily be opposed by pointing out that 'normality' can be challenging to define and 'normal' is not necessarily equivalent with 'good'.

Another answer is that the removal of a disease can be seen as a way to restore equality, whereas human enhancement is more likely to increase inequality. This is significantly harder to dismiss, but also this distinction can be contested. Gene technology is likely to be unequally distributed and may be available only for the 'rich and privileged' people, but as we saw in chapter 5, it has been argued that the mere fact that some people will not be able to afford it does not give justifiable reason to deny those who can afford the technology to use it. Also, as Resnik (1994) has pointed out, the enhanced characteristics of some people are likely to also benefit the 'non-enhanced'. For example, if people with enhanced intelligence use their ability to develop new and improved medical treatments or technology, this may increase the overall welfare in a society.

Why not perfect?

If the technology improves to the extent that we can change virtually any phenotype we want, should we aim for perfection? Savulescu and Kahane (2009) argue that it is a parental obligation to aim to have the best child possible. The Principle of Procreative Beneficence (PPB) holds that:

> If couples (or single reproducers) have decided to have a child, and selection is possible, then they have a significant moral reason to select the child, of the possible children they could have, whose life can be expected, in light of the relevant available information, to go best or at least not worse than any of the others (Savulescu & Kahane, 2009 p. 274)

This approach has been widely criticized for many reasons. One of the problems is the difficulty in answering the questions '*what is perfect?*' and '*what is the best life?*'. There is no universal answer to what characteristics will give the best chance to the best life. So how can parents possibly know what the best life for their child will be? Savulescu (2001) points out that he understands 'the best life' as "the life with the most well-being" (p. 419), but that does not solve the problem given the fact that well-being is also highly subjective. This is problematic in several ways. First and foremost, it may put an unreasonably high pressure on the parents. The parents might be so preoccupied with finding 'the best' that they overlook other forms of a good life, and 'the best' may not be what is actually best for the child. The child's right to an open future may thus be violated in the parents' pursuit for 'perfect' (Glover, 2006).

> [A]iming at the best is compatible with thinking that the concept of the most advantaged life is plural and open-ended. If different forms of life are equally good, or if the amount of well-being realized in each is incomparable, then parents can reasonably choose either option. But there are plenty of cases where we can rank the goodness of lives. We do so in numerous moral decisions in everyday life, especially in bringing up and educating our children (Savulescu & Kahane, 2009, p. 279)

Additional difficulties in determining 'the best' characteristics are caused by the importance of varying environmental conditions in which advantageous genetic traits will differ, and the genome that gives 'the best chance to the best life' will thus vary depending on the environment the child will grow up in (Sparrow, 2011). A particular trait may be valued differently in different environments and societies. The value of a trait may also be dependent on what Buchanan et al. (2000) called *'complementarity'*, meaning "the existence, in sufficient numbers, of persons with other traits with which they can be combined in cooperative interactions" (p. 80).

> For our own and our children's sakes, such statements by enhancement supporters of the need to articulate substantive notions of "well-being and the good life" must not remain unfulfilled promissory notes. The question we should address more concertedly is, for the sake of what, if anything, could the pursuit of vigorous cognitive enhancement be justified? Because the controversy over enhancement is ultimately about values as reflected in aspirations and ideals, reframing the debate to foreground this fact would itself be a marked advance (Levin, 2017 p. 42)

The idea of a good life is perhaps easier to comprehend in terms of what does *not* count as a good life. In that case, the perfectionist approach can be understood as 'it is a prima facia obligation to create offspring that will not have a 'condition' (i.e., genetic trait, disease, disability, etc.) that does *not* count as a good life. In other words, there is a prima facie obligation to create a child without any disadvantages. This might make the perfectionist approach more plausible, albeit some of the issues with this approach will still be present. It may also be some disagreement about what does *not* count as a good life. For instance, the good life for a masochist might involve some pain, although pain is normally seen as something that does *not* count as a good life for most people.

What the best chance of the best life is will almost certainly be influenced by the society and perhaps even by unjust social norms. Given that it is an obligation to create a child with the best chance to the best life, the unjust social norms must also be considered, and the child's genetic characteristics should thus be chosen according to this. It may, for instance, be permitted

to choose to have a boy in a sexist community or a fair-skinned child in a racist community. This is likely to exacerbate the unjust social norms even further and thereby increase discrimination and inequality. Savulescu and Kahane (2009) have, however, stated that:

> The reasons given by PB can be defeated or outweighed by other moral reasons. Many would say that they would be defeated in this case. Parents shouldn't choose the fair skinned child because of the expected prejudice. It's better to change pernicious attitudes than to reinforce them through capitulation (p. 290).

This may, however, be a bit too optimistic. It is likely that some people would choose their children's genetic characteristics according to the attitudes in the society because it will perhaps be the 'easiest short term solution'. Everyone wants the best for their child, and the negative effect of their actions tend to be less important as long as it increases their child's well-being.

To conclude, the obligations parents have to give their child a good life would permit germline editing to prevent genetic disease. It may also be seen as a prima facie obligation to prevent genetic disease if it is not too demanding. Germline editing for enhancement purposes is, on the other hand, much more ethically challenging and should not be permitted.

CONCLUSION

SHOULD WE EDIT THE HUMAN GERMLINE?

The aim of this thesis was to analyze the permissibility to abstain from human germline editing on the premise that the technology is sufficiently safe. The thesis has focused on the following key question:

- ***Are the ethical issues with human germline editing sufficient to justify a ban on potentially life-saving technology?*** No. The ethical arguments against germline editing are almost exclusively related to human enhancement. On the premise that it is possible to draw a line between therapy and human enhancement, there is a long way from curing catastrophic genetic diseases to enhance human capacities. As discussed in Chapter 4, this line can, for instance, be drawn based on normal gene function: genetic interventions that correct a mutated gene to restore the gene's normal function are therapy, whereas edits in genes where there is no mutation to be corrected are human enhancement. Genetic enhancement is not yet feasible due to technological challenges and limits in our knowledge about genotype-phenotype correlation. And even if genetic enhancement could be done, the fact that the technology can be used for genetic interventions beyond what is considered morally permissible does not justify banning the use of the technology.
- ***What are our moral obligations when creating a child?*** It is a moral obligation to ensure that the child is not harmed and that it gets medical treatment if necessary. This obligation could also include prevention of harmful medical conditions prior to birth and that disease and disability should be prevented whenever it is possible. A ban on germline editing may thus be seen as a violation of the moral obligation to prevent harm and may even be seen as a violation of human rights. It is, for example, a fundamental human right to have "the highest attainable standard of health" (World Health Organization, 1948). Although the concept of 'health' is disputed, it is safe to presume that it includes avoiding adverse genetic diseases.
- ***To what extent should parents be allowed to decide what type of child they want?*** Parents should be allowed to choose not to have a child with a disease or disability, but they should

not be allowed to choose their child's genetic characteristics beyond what is seen as medical. One reason for this is that they cannot possibly know what their child will desire and value later in life. Human enhancement raises numerous ethical concerns, and germline editing should therefore be limited to curing harmful medical conditions.

The germline editing debate is a minefield of perplexities and moral dilemmas. Many of the arguments that are used against germline editing can also be used to advocate for germline editing. One can, for instance, argue that germline editing interferes with the child's right to create its own future, but it can also be argued that it can promote the child's right to an open future by giving it the capacities and abilities it needs to pursue their desires. Also, being born with severe disease and disability has a tremendous impact on the child's right to an open future. The same goes for the arguments that allowing germline editing is likely to increase inequality; germline editing can also be used to promote equal opportunity by leveling the playing field for those who are worst off. Whether these arguments are perceived as reasons to allow or to prohibit germline editing is primarily up to subjective interpretations. In defiance of great variety, our subjective perception is strongly influenced by culture, religion, traditions, etc., and will – at least to a certain degree – be shared among people in the same community. Many have, however, emphasized the need for global deliberation with the aim to achieve a broad societal consensus on the regulation of human germline editing and (potentially) the future of the human species (Howell et al., 2020; Jasanoff & Hurlbut, 2018).

Moral particularity is crucial for further assessment and establishment of guidelines that ensure safety and simultaneously uphold scientific progress. Every possible application and case is different – just as every gene is different – and must be assessed vis-à-vis all the biological and circumstantial factors. Biological (i.e., phenotypical) consequences may vary among genes due to phenomena such as epistasis (multiple genes interact to express one phenotypic trait) and pleiotropy (one gene affects several phenotypic traits), and every disease and disability differ in symptoms, available treatment, prognosis, severity, etc. The burden of the disease and disability will also differ in every case due to subjective interpretations and differences in available resources. For instance, paralysis may be easier to cope with for those who have access to assistance and support and for those who live in communities where the environment is adapted to reduce the impairment of disabilities.

There are still some technological challenges and risks that remain to be solved, and further research is necessary to ensure that germline editing is sufficiently safe (see Chapter 3). Full elucidation of potential risks may not be possible before clinical trials due to the

requirement to terminate the experiment within a short timeframe after fertilization (14 days in Norway). Given the severity of many of the genetic diseases, it may be justifiable to proceed to clinical trials despite some unresolved risks as long as the benefits outweigh the risks.

To conclude, it is not just ethically justifiable to permit germline editing but a moral imperative. CRISPR/Cas gene technology is powerful, and it is crucial to proceed with caution, but it is nonetheless important to proceed with the research and, eventually, also clinical trials when (or *if*) it is confirmed that the risks do not outweigh the benefit. One should be cautious about the ethical concerns, but it is important to not let speculations and irrational fear about what may or may not happen blind us to the true benefits of germline editing.

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