Master's Thesis

A *CRISPY* FUTURE AHEAD FOR CRISPR-HUMANS?

The rationales that could be taken into account by the EU when regulating clinical applications of CRISPR-Cas9 on humans.

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“One small step for a man, one giant leap for mankind."

– Neil Armstrong, *first person to walk on the Moon* (1969).

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1. Introduction

According to Stephen Hawking, "superhumans" would be the human species that will end humanity. In his posthumous book, Hawking reveals an apocalyptic theory about gene-edited humans.[1] The use of genome engineering technology CRISPR-Cas9 (also referred to as "CRISPR") is one of the drivers behind his reasoning. Hawking's book symbolizes the ethical and societal sensitivity of human genome engineering. This sensitivity is also visible in the legislative landscape, as legislation on human genome modification is scattered globally due to the fact that legislators have not been able to reach consensus on how to regulate human genome modification.[2] In that regard, this thesis will focus on providing the rationales that could form the bases for regulating, in the European Union (also referred to as "EU"), clinical applications of genome engineering technology CRISPR-Cas9 on humans.

1.1 Background

1.1.1 Problem definition

A mere twenty years ago, the modification of human genomes seemed to be science-fiction. The movie *Gattaca* (1997) illustrates this idea particularly well. Mostly, *Gattaca* draws attention to technologies that can be used to edit the human germ line, in order to design humans according to their wishes, so that only the *desir*ed genes are passed on to future generations. The movie addresses the possible (undesirable) consequences of designing humans. Up and till today, this still may sound like science-fiction to the majority of the people. However, if CRISPR-Cas9 manages to live up to its potential, science-fiction scenarios as projected in the *Gattaca* movie might be feasible.

CRISPR-Cas9 is a revolutionary technology that allows for genome engineering. Through CRISPR-Cas9, scientists are able to target and cut out any material in the DNA in an accurate and precise manner.[3] The alleged accurateness and preciseness of CRISPR-Cas9 distinguishes it from conventional GETs.[4] According to scientists, CRISPR-Cas9 has enormous potential. It could, *inter alia*, prevent or even cure diseases such as various types of cancer, HIV, and

[1] In Hawking's posthumous book, "superhumans" means gene-edited humans; S Hawking, *Brief Answers to the Big Questions* (First, Bantam Books, New York 2018).

[2] R Isasi, E Kleiderman and BM Knoppers, 'Editing Policy to Fit the Genome? Framing Genome Editing Policy Requires Setting Thresholds of Acceptability' (2016) 351 Science 337; Jeff Kipling, 'The European Landscape for Human Genome Editing - A Review of the Current State of the Regulations and Ongoing Debates in the EU' (2016).

[3] Jennifer A Doudna and Emmanuelle Charpentier, 'The New Frontier of Genome Engineering with CRISPR-Cas9' (2014) 346 Science 1077; Arthur L Caplan and others, 'No Time to Waste--the Ethical Challenges Created by CRISPR: CRISPR/Cas, Being an Efficient, Simple, and Cheap Technology to Edit the Genome of Any Organism, Raises Many Ethical and Regulatory Issues beyond the Use to Manipulate Human Germ Line Cells' (2015) 16 EMBO reports 1421.

[4] Conventional genome engineering technologies in this regard are ZFNs and TALENs; Caplan and others (n 3).

Malaria. Moreover, scientists claim that human genomes could be modified in a manner that allows hereditary diseases not to be passed on to descendants.[5]

However, CRISPR-Cas9 technology sparks controversy as well, in general, and when applied to humans. As mentioned above, CRISPR-Cas9 allows for the modification of (human) genes. Depending on which type of genes are modified, these modifications could be passed on to future generations and could have (unforeseeable) consequences. CRISPR-Cas9 could be used for so-called *enhancement purposes*, which essentially means the genetic enhancement of particular individuals of society. Thus, it could lead to severe inequalities, resulting in a different type of *classes* of humans.[6] A more general controversy around CRISPR-Cas9 is that interference with natural human evolution could be considered irresponsible.[7] Moreover, according to scientists, CRISPR-Cas9 is prone to misuse, which constitutes a significant threat as CRISPR-Cas9 is relatively cheap, and therefore, accessible.[8]

Up and till today, the enhancement or treatment of living organisms by employing GETs, in general, remains a controversial and delicate subject.[9] The CRISPR-Cas9 technology has been widely applied in scientific research on other living organisms. For instance, research has been conducted on mice, demonstrating successful results, as the mice appeared to have restored dystrophin expression and improved muscle function.[10] Researches like those mentioned above, open(ed) the door to the clinical applications of CRISPR-Cas9 on humans. However, it seems so that clinical applications of CRISPR-Cas9 on humans (on a broad scale) are becoming a reality. Proof of that is that the first research on the clinical application of CRISPR-Cas9 on humans *in vivo* has already been conducted in China in 2015.[11] Even in Europe, particularly in the United Kingdom and Sweden, the first researches on applying CRISPR-Cas9 on human *in vivo* embryos have also already been approved by the respective governments.[12] At the time of writing (late November 2018), a Chinese scientist claimed to have successfully applied CRISPR-Cas9 to embryos, resulting in "CRISPR-babies".[13]

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[5] Doudna and Charpentier (n 3); David Baltimore and others, 'A Prudent Path Forward for Genomic Engineering and Germline Gene Modification' (2015) 348 Science 36; Katrine S Bosley and others, 'CRISPR Germline Engineering—the Community Speaks' (2015) 33 Nature Biotechnology 478; Caplan and others (n 3).

[6] Bosley and others (n 5); Giovanni Rubeis and Florian Steger, 'Risks and Benefits of Human Germline Genome Editing: An Ethical Analysis' (2018) 10 Asian Bioethics Review 133.

[7] Bosley and others (n 5); Rubeis and Steger (n 6).

[8] Bosley and others (n 5); Rubeis and Steger (n 6).

[9] Jeantine Lunshof, 'Regulate Gene Editing in Wild Animals' (2015) 521 Nature 127.

[10] Chengzu Long and others, 'Postnatal Genome Editing Partially Restores Dystrophin Expression in a Mouse Model of Muscular Dystrophy' (2016) 351 Science 400.

[11] Puping Liang and others, 'CRISPR/Cas9-Mediated Gene Editing in Human Tripronuclear Zygotes' (2015) 6 Protein and Cell 363.

[12] Ewen Callaway, 'Gene-Editing Research in Human Embryos Gains Momentum' (2016) 532 Nature 289.

[13] Antonio Regalado, 'EXCLUSIVE : Chinese Scientists Are Creating CRISPR Babies' (*MIT Technology Review*, 2018) <https://www.technologyreview.com/s/612458/exclusive-chinese-scientists-are-creating-crispr-babies/> accessed 25 November 2018; The scientist claimed that he was able to eliminate the CCR5 gene from the human gene-line. The CCR5 gene is believed to be a gene that causes of HIV, smallpox and cholera. By eliminating the CCR5 gene, the scientist planned to render the offspring resistant to HIV, smallpox, and cholera. According to the scientist, this resulted in healthy, gene-edited and "HIV-free" babies, which were actually born.

Following the first researches in 2015, renowned scientists in the field of biotechnology from around the world published a statement, in which they affirmed that human genome engineering is irresponsible until a broader societal consensus is achieved on the appropriateness of employing GETs for clinical applications on humans.[14] As a consequence of the latest CRISPR-Cas9 experiment on babies, in which Chinese scientist He Jiankui claimed to have successfully eliminated the CCR5 gene out of the human gene-line, this statement seems to be reaffirmed: scientists from around the globe condemn the latest CRISPR-Cas9 experiment[15], and about 120 Chinese scientists deem the latest CRISPR-Cas9 experiment as "crazy".[16] On top of that, due to these recent developments, renowned scientists[17], as well as the United Nations (also referred to as "UN")[18], reiterated the call for a moratorium on germ line modifications of human genomes, as well as the call for global rules on human genome modifications.

The controversy of clinical applications of CRISPR-Cas9 on humans is also visible in the legal realm. As research shows, and as will be explained below, there is significant fragmentation in the legal frameworks globally and at the EU level.[19] In line with the research mentioned above, the conclusion can be drawn that legislators have not been able to achieve consensus on the regulation of human GETs.

1.1.2 Literature survey

CRISPR-Cas9 can be used on all organisms living on the Earth, such as plants, animals, and humans. For this thesis, an account will be given of the literature solely regarding the application of CRISPR-Cas9 for clinical applications on humans.

However, the majority of the produced literature regarding clinical applications of CRISPR-Cas9 on humans is generally related to the technical aspects (biotechnological literature) and

[14] David Baltimore and others, 'On Human Gene Editing: International Summit Statement', *International Summit on Human Gene Editing* (2015).

[15] Dan Robitzski, 'Scientists Around the World Condemn That CRISPR Baby Experiment' (*Futurism*, 27 November 2018) <https://futurism.com/scientists-condemn-crispr-baby-experiment/> accessed 27 November 2018.

[16] Akshat Rathi and Echo Huang, 'Chinese Scientists Condemn CRISPR Baby Experiment as "Crazy"' (*Quartz*, 2018) <https://qz.com/1474530/chinese-scientists-condemn-crispr-baby-experiment-as-crazy/> accessed 26 November 2018.

[17] Eric S Lander and others, 'Adopt a Moratorium on Heritable Genome Editing' (2019) 567 Nature 165; Antonio Regalado, 'CRISPR Inventor Feng Zhang Calls for Moratorium on Gene-Edited Babies' (*MIT Technology Review*, 2018) <https://www.technologyreview.com/s/612465/crispr-inventor-feng-zhang-calls-for-moratorium-on-baby-making/> accessed 28 November 2018; Michael Le Page, 'Top Geneticist Calls for Global Rules for Ethical Human Genome Editing' (*New Scientist*, 2019) <https://www.newscientist.com/article/2189802-top-geneticist-calls-for-global-rules-for-ethical-human-genome-editing/> accessed 8 January 2019.

[18] Jamey Keaten and Maria Cheng, 'UN: Gene Editing for Human Reproduction Is "Irresponsible"' (*The Associated Press*, 2019) <https://www.apnews.com/32d57608d19a48caa68c182b64c6edab> accessed 19 March 2019.

[19] Isasi, Kleiderman and Knoppers (n 2); Kipling (n 2).

the social and ethical aspects (bioethical literature) thereof. In the bioethical literature, scholars give an analysis of the regulation of CRISPR-Cas9 for clinical applications. Conversely, there is a lack of literature relating to the legal aspects of clinical applications of CRISPR-Cas9 on humans.

Quantitative researches by Isasi, Kleiderman, and Knoppers, as well as Kipling, show that there is little to no harmonization of rules on human genome engineering, as countries to a large extent set out different rules.[20] Both researches show that there are numerous legal interventions (e.g. number of pieces of legislation) and types of regulations (e.g. guidelines or more binding rules), either at state-level or super-state level. Additionally, they claim that the EU and CoE legal frameworks governing human genome engineering, are not *sufficient* nor *effective* to regulate clinical applications CRISPR-Cas9 on humans.[21] This is due to the very nature of the CRISPR-Cas9 technology, which makes it possible to circumvent existing legislation, as the technology is relatively inexpensive and, therefore, highly accessible.

To a large extent, the inability to achieve (legislative) consensus globally, has to do with the ethical and social controversy regarding human genome engineering. This is also made more complicated by the fact that ethics diverge based on culture, economics, and geographic location. The research found that the preferences of counties diverge extensively, but also correlate significantly with culture and economics. In essence, the research provided an insight into the (collective) ethical priorities that exist within different cultures around the globe. It concluded that cultural ethics diverge based on culture, economics, and geographic location.[22] The recent developments in the research and application of CRISPR-Cas9 on humans have only seemed to strengthen this controversy.[23] According to the literature, and as will be explained in the following chapter, the main ethical and social controversies are, among others, as also mentioned above, the damage to future generations of humans, that enhancement of

[20] Isasi, Kleiderman and Knoppers (n 2); Kipling (n 2); Alexandre Angers and others, 'Overview of EU National Legislation on Genomics' (2018).

[21] Kipling (n 2).

[22] Edmond Awad and others, 'The Moral Machine Experiment' (2018) 563 Nature 59; The MIT conducted as research and launched the so-called "Moral Machine". Through the experiment with the "Moral Machine, over two million people from 233 countries participated. In the experiment, participants were asked to make decisions on which lives self-driving cars should prioritize, by means of different variations of the "trolley problem". The "trolley problem" is a classic thought experiment, which is performed in the realm of ethics. The "trolley problem" provides for a dilemma in which one has to decide what is the more ethical option. The classic "trolley problem" dilemma goes as follows. A picture is shown with on it a runaway (or track) on which a trolley is moving forward whilst there are five persons tied-up and lying on the main track and one person tied-up and lying on a side track. The person who is undergoing the "trolley problem" dilemma is standing next to a lever that controls a switch. One is forced to make a choice: do nothing and the trolley will keep on going on the main track and will kill the five persons, or, pull the lever, which makes that the trolley will go to the side track and kill the one person. The "Moral Machine" experiment used the "trolley problem", replaced the trolley with a self-driving car, and tested nine different situations. This research could also provide for an explanation as to why there is a great difference in the legal frameworks of countries, as it could be the case that, based on cultural differences, each country takes a different stance towards what is acceptable with regard to human genome modifications.

[23] Robitzski (n 15); Rathi and Huang (n 16); Regalado, 'CRISPR Inventor Feng Zhang Calls for Moratorium on Gene-Edited Babies' (n 17).

humans will create different societal classes, the misuse of the technology due to its accessibility, and the general idea of interfering with natural human evolution.[24] Counterarguments to the ethical and social controversy on human genome engineering are generally related to the potential of the CRISPR-Cas9 technology, as briefly mentioned before.[25]

1.1.3 Aim of thesis/significance

This thesis aims to provide legislators in the EU with a conceptual basis in order to regulate clinical application of CRISPR-Cas9 on humans. This thesis will do so by providing rationales. In order to achieve the previous, this thesis will first assess the issues and their relevance from the ethical and societal perspectives to the employment CRISPR-Cas9 for clinical applications on humans. After that, this thesis will examine the existing EU and CoE, but also the UN, legal frameworks governing human genome engineering. It will provide an insight into the legal frameworks and it will analyse which existing rationales can be derived from it in order to regulate CRISPR-Cas9 for clinical applications on humans. Subsequently, this thesis will examine which additional rationales could be added to the rationales that form the underlying basis of the existing UN, EU and CoE legal frameworks to human genome engineering and can be used to regulate CRISPR-Cas9.

1.2 Research questions

1.2.1 Central research question

In order to achieve the aim of this thesis, as mentioned above, the central research question that guides this thesis is as follows:

"*Which rationales could the EU take into account when regulating clinical applications of genome engineering technology CRISPR-Cas9 on humans?*".

1.2.2 Sub-questions

To answer the central research question of this thesis, as mentioned above, sub-questions will be used. The sub-questions that will be used for this thesis are as follows:

1) What is genome engineering technology CRISPR-Cas9, and how is it employed on humans for clinical applications?

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[24] Rubeis and Steger (n 6); Stella K Vasiliou and others, 'CRISPR-Cas9 System: Opportunities and Concerns' (2016) 62 Clinical Chemistry 1304; Diana Gulei and Ioana Berindan-Neagoe, 'CRISPR/Cas9: A Potential Life-Saving Tool. What's Next?' (2017) 9 Molecular Therapy - Nucleic Acids 333; Rodolphe Barrangou and Andrew P May, 'Unraveling the Potential of CRISPR-Cas9 for Gene Therapy' (2015) 15 Expert Opinion on Biological Therapy 311.

[25] Caplan and others (n 3); Rongxue Peng, Guigao Lin and Jinming Li, 'Potential Pitfalls of CRISPR/Cas9-Mediated Genome Editing' (2016) 283 FEBS Journal 1218; Vasiliou and others (n 24); Rubeis and Steger (n 6); Martina Baumann, 'CRISPR/Cas9 Genome Editing – New and Old Ethical Issues Arising from a Revolutionary Technology' (2016) 10 NanoEthics 139; Edward Lanphier and others, 'Don't Edit the Human Germ Line' (2015) 519 Nature 410; Christopher A Lino and others, 'Delivering CRISPR: A Review of the Challenges and Approaches' (2018) 25 Drug Delivery 1234.

2) What are the issues at ethical and societal level deriving from the clinical applications of CRISPR-Cas9 on humans?
3) What provisions, that are relevant for regulating clinical application of CRISPR-Cas9 on humans, do the existing UN, EU, and CoE legal frameworks regarding human genome engineering hold?
4) Which rationales that underlie the existing UN, EU, and CoE legal frameworks regarding human genome engineering, could be used to regulate clinical application of CRISPR-Cas9 on humans, bearing in mind posed perspectives that are examined?
5) Which additional rationales could be added to the UN, EU, and CoE legal frameworks regarding human genome engineering, to regulate clinical applications of CRISPR-Cas9 on humans?

1.3 Methodology

1.3.1 Methods

This thesis is a doctrinal/theoretical research whose purpose it is to provide EU legislators with rationales that should be used in order to regulate the gene-technology CRISPR-Cas9 for clinical applications on humans. In order to do so, the following methodology was applied.

As regards to sub-questions 1 and 2, the answers to these questions will form the basis of this research as they give a concept of the CRISPR-Cas9 technology and identify the issues deriving from clinical applications of CRISPR-Cas9 on humans. This baseline is necessary in order to identify which issues need to be mitigated when regulating clinical applications of CRISPR-Cas9 on humans. The research regarding these sub-questions was conducted by consulting text-based sources, such as (journal) articles and books. Regarding the nature of these sources, it is important to note that merely authoritative sources were consulted. This means that merely sources of which the authors are considered experts or authorities in the relevant fields of expertise were consulted. These authors are, *inter alia*, J. Doudna, E. Charpentier, F. Zhang, D. Baltimore, H. Greely, T. Ishii, R. Isasi, M. Araki, and J. Kipling.

With reference sub-question 3, the answers to this question aim to chart the existing legal frameworks regarding human genome engineering. It is the purpose of this thesis to provide legislators in the EU with rationales that could be taken into account when regulating clinical application of CRISPR-Cas9 on humans. Therefore, this sub-question will merely analyse standard-setting and principle-setting treaties, viz. the UNESCO Universal Declaration on Bioethics and Human Rights (also referred to as UDBHR), the UNESCO Universal Declaration on the Human Genome and Human Rights (also referred to as UDHGHR), and Convention on Human Rights and Biomedicine (also referred to as *Oviedo Convention*). All the aforementioned treaties are standard-setting and principle-setting treaties and, therefore, by their nature suit best to derive rationales from. Moreover, the majority of EU Member States are a participant in either, or both, the UNESCO treaties or/and the *Oviedo Convention*.[26] The research regarding this sub-question was conducted by consulting text-based sources, such as

[26] Henk AMJ Ten Have and Bert Gordijn, *Handbook of Global Bioethics* (Springer 2014).

(literature on) international treaties and legislation, as well as law books and legal journal articles. Regarding the nature of these sources, it is important to note that merely authoritative sources were consulted. This means that merely sources of which the authors are considered experts or authorities in the relevant field of law were consulted. These authors are, *inter alia*, H. ten Have, B. Gordijn, M. Jean, R. Andorno, E. Pellegrino, M. Neves, M. Morisaki, and H. Nys.

Concerning sub-question 4, the answers to this question aim to identify which rationales, that underlie the existing UN, EU and CoE legal frameworks governing human genome engineering, could be used in order to address the issues deriving from clinical applications of CRISPR-Cas9 on humans. This was done by analysing which rationales, and what extent, are able to address the issues deriving from clinical applications of CRISPR-Cas9 on humans. As further on in this thesis will be explained, not all issues deriving from clinical applications of CRISPR-Cas9 on humans can be addressed by the rationales that underlie the existing UN, EU, and CoE legal frameworks. Concerning those issues, sub-question 5 aims to add additional rationales, by stating the additional issues that could be taken into account by the EU when regulating clinical applications of CRISPR-Cas9 on humans.

1.3.2 Outline/structure

This thesis will be structured as follows. First, in Chapter Two, a description will be provided on what the CRISPR-Cas9 technology is about and how the CRISPR-Cas9 technology is (or can be) applied for clinical applications on humans. Moreover, an insight into the use of CRISPR-Cas9 for clinical applications on humans will be given from a legal, ethical, and social perspective. Subsequently, in Chapter Three, an account will be given of the existing European (e.g. EU and CoE) and the UN legal framework on human genome engineering. Thereafter, in Chapter Four, an analysis of the rationales that could be taken into account when regulating clinical applications of CRISPR-Cas9 on humans that derive from the existing UN, EU and CoE legal frameworks, and address the issues as mentioned in Chapter Two, will be given. Additionally, an analysis of additional rationales that could be taken into account when regulating clinical applications of CRISPR-Cas9 on humans, which are not addressed by the existing UN, EU and CoE legal frameworks will be given. Finally, in Chapter Five, the abovementioned central research question will be answered in the form of a conclusion, by combining the answers to the sub-question that are provided in each core chapter.

2. CRISPR-Cas9 and clinical applications on humans

This chapter provides an overview of the CRISPR-Cas9 technology and how it is applied to humans. First, it explains what human genome engineering is, how it can be applied, and what the purposes for application on humans are. Further on, an explanation is provided on how the CRISPR-Cas9 technology works and what its significance is. Finally, the different perspectives that there are concerning the application of CRISPR-Cas9 on humans will be briefly analysed. In that regard, a multidisciplinary perspective is used.[27]

2.1 Human genome engineering

The field of genome studies genes and their functions, as well as techniques that are related to those functions, whereas the field of genetics studies heredity.[28] Genome engineering technologies offer the potential for modifying human and nonhuman genomes.[29] Essentially, genome engineering (also referred to as "genome editing" and "genome modification"), is a specific form of genetic engineering. Through genome engineering, it is possible to make changes in the DNA of living organisms. Genome engineering relies on the principle of "site-specific recognition of DNA sequences", which means that specific changes can be made to the genomes of cells and organisms. In this manner, genome engineering allows modification, replacement, deletion, and insertion of genomes to human cells.[30]

2.1.1 Somatic and germ line applications (on humans)

Genome engineering facilitates the possibility to change somatic cells, as well as the nuclei of reproductive cells, which is also referred to as an organism's "germ line" (also see Figure 1). As a result of modifications to the nuclei of reproductive cells, or germ line, the altered cells covey their information from their own generation of cells to the next generation of cells. Hence, germ line modification entails the possibility to alter the genetic makeup of cells that will be passed on to its descendants.[31] In contrast, the modification of somatic cells does not entail that the altered cells convey their information to the next generation of cells. Essentially, when the organism dies,

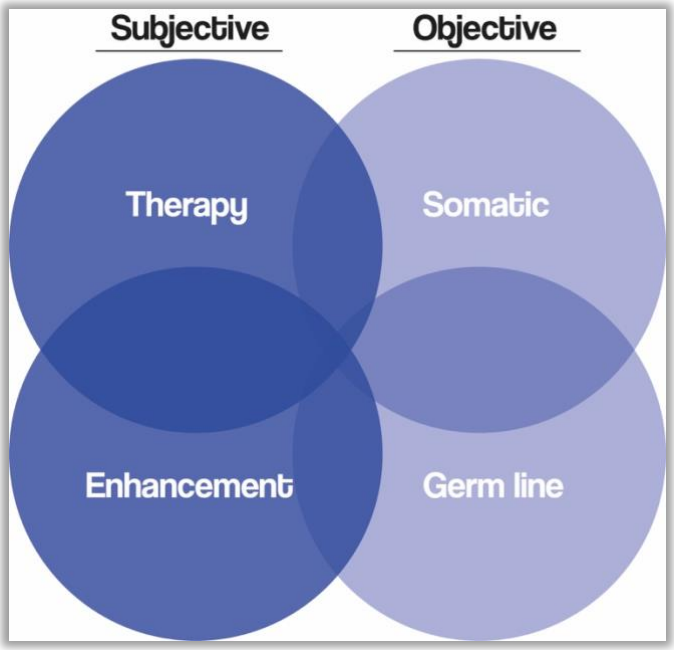

Figure 1 - Applications and purposes of genome engineering

[27] This chapter will provide an insight into the scientific, technological, ethical, societal, and legal perspectives.

[28] World Health Organization, 'WHO Definitions of Genetics and Genomics' (*WHO*, 2016) <https://www.who.int/genomics/geneticsVSgenomics/en/>.

[29] Baltimore and others (n 5).

[30] Doudna and Charpentier (n 3).

[31] Baltimore and others (n 5).

the altered, somatic cells die with it. Thus, through the modification of somatic cells, it is not possible to alter the genetic makeup of future generation cells.[32] These applications can also be referred to as the "objective element" of genome engineering, as it is objectively determinable to assess which type of cell is modified, and no subjective interpretation by humans is needed.

2.1.2 Therapeutical and enhancement purposes

Next to the "objective element" of genome engineering, there is the so-called "subjective element" of genome engineering. This is where the subjective interpretation of humans comes into play. It concerns the purpose of modification of somatic or germ line cells. A difference in the purposes can be made into therapy purposes (also referred to as "medical") and enhancement purposes (also referred to as "non-medical") purpose (also see Figure 1). The therapeutical or medical purpose signifies genome engineering for the purpose of disease-curing or disease-prevention, whereas the enhancement or non-medical purpose signifies genome engineering for the purpose of improving the human species.[33] When the "objective element" and "subjective element" of human genome engineering are combined, a plethora of ethical and social frictions and discussions arise. These ethical and social frictions will be elaborated further on in this chapter.

2.2 Concept of CRISPR-Cas9 technology

2.2.1 Explanation of the technology

CRISPR-Cas9 is one of the existing genome engineering technologies. The CRISPR-Cas9 technology can be divided into two separate elements, which are CRISPR and Cas9. CRISPR stands for Clustered Regularly Interspace Palindromic Repeats, which are essentially repeating cluster sequences in an organisms' DNA. Scientists discovered that the clusters served a crucial function, as they were part of a bacteria's immune system. It was discovered that, after a bacterium is infected by a virus, it is able to "store" residue of the virus within these CRISPRs. After the storing of the residue within the CRISPRs, these series of clusters are stored within the genome of the bacteria. By storing all the "information" in its genome, bacteria are able to defend themselves in the future against the same virus. In order to defend itself, bacteria use an enzyme to remove the virus from the genome. The enzyme which the bacteria (typically) uses is called Cas9.[34] CRISPR-Cas9 works much like a fingerprint database owned by the police: once a criminal has his fingerprint stored in the police database and then commits a new crime, the database will recognize his fingerprint as matching those already in the database.

After scientists discovered that CRISPR-Cas9 could be used to provide immunity against future viruses, they started experimenting programming CRISPR to use it in other organisms. This process entails only two steps. First of all, scientists "program" a specific DNA sequence, which will be the "guide" molecule (also known as "RNAs"). They will target the precise position on the DNA double helix where the modification is required and then they will align

[32] ibid.

[33] ibid; Tetsuya Ishii, 'Germline Genome-Editing Research and Its Socioethical Implications' (2015) 21 Trends in Molecular Medicine 473.

[34] Doudna and Charpentier (n 3).

the guide molecule with that exact position. The second step is that, once the guide molecule is deployed, it will guide CRISPR to that exact position on the DNA double helix. Once the CRISPR has reached the designated position, it will cut open and split either strand of the DNA's double helix. This allows the enzyme, Cas9, to remove the designated sequence from the genome.[35]

2.2.2 Technological and general significance

CRISPR-Cas9 is not the first genome engineering technology. Instead, before CRISPR-Cas9, there were already other genome engineering technologies. The first engineering technology was zincfinger nucleases (hereafter: ZFNs). ZFNs are expensive, time-consuming to engineer, and very complex. Years after the introduction of ZFNs, a second genome engineering technology known as transcription activator-like effector nucleases (hereafter: TALENs) was developed. TALENs are similar to ZFNs but more flexible as they can target larger DNA sequences.

	ZFNs	TALENs	CRISPR
Cost	High	High	Low
Complexity	Difficult	Difficult	Easy
Multiple edits	Difficult	Difficult	Easy

Figure 2 - Comparison of genome engineering technologies

Meanwhile, in another field of research, CRISPR-Cas9 was discovered. In comparison to ZFNs and TALENs, CRISPR-Cas9 allows for more "edits", as it does not require substantial protein engineering. CRISPR-Cas9 only requires an RNA (also see Figure 2).[36] Moreover, CRISPR-Cas9 is unique because it enables exact genome engineering, as it allows for precise and efficient targeting, modification, and regulation of a wide array of genomes. Additionally, CRISPR-Cas9 is relatively inexpensive and easy to use. Hence, CRISPR-Cas9 was widely and rapidly adopted by the scientific community and triggered a revolution, with innovative applications in biology.[37]

The technology was named *Science* magazine's Breakthrough of the year in 2015.[38] Moreover, the *MIT Technology Review* described CRISPR-Cas9 as "the biggest biotech discovery of the century".[39] The CRISPR-Cas9 technology had (or has) a significant impact in the scientific realm. According to bio scientists, CRISPR-Ca9 allows for researches that were not possible before. These scientists claim that CRISPR-Cas9 advance experimental biology in an

[35] ibid.

[36] ibid; 'Edits' means, in this regard, how many times one CRISPR-Cas9 set can be exploided untill it is exhausted and a new set needs to be engineered.

[37] ibid; Baltimore and others (n 5).

[38] John Travis, 'Making the Cut: CRISPR Genome-Editing Technology Shows Its Power' (2015) 350 Science 1456.

[39] Antonio Regalado, 'Who Owns the Biggest Biotech Discovery of the Century?' (*MIT Technology Review*, 2014) <https://www.technologyreview.com/s/532796/who-owns-the-biggest-biotech-discovery-of-the-century/>.

unprecedented manner. Due to CRISPR-Cas9, scientists gained a better understanding of how genomes develop, what genomes' physiology is, and how genomes hinder diseases.[40] Because of the fact the CRISPR-Cas9 technology is a precise and efficient manner to examine and modify genomes, scientists gained extensive information about genomes. Scientists would not have gained this information if CRISPR-Cas9 did not exist.[41]

Lastly, CRISPR-Cas9 is deemed "to change medicine forever".[42] According to scientists, CRISPR-Cas9 would potentially be able to provide as a treatment or therapy for major diseases, amongst others, various types of cancers, such as lung cancer, acute myeloid leukaemia, Ewing's sarcoma, liver cancer. Moreover, CRISPR-Cas9 would potentially be able to correct genetic mutations that are responsible for inherited disorders. This means that CRISPR could be used as a gene therapy to treat genetic disorders.[43]

2.3 Issues deriving from clinical applications of CRISPR-Cas9 on humans

In this paragraph, a multidisciplinary approach will be taken in order to identify the issues driving from clinical applications of CRISPR-Cas9 on humans at ethical and societal levels.

Besides the tremendous potential, briefly explained in the previous paragraph, CRISPR-Cas9 has its pitfalls as well. One of these pitfalls regards the safety and reliability of the technology. At this moment in time, scientists cannot guarantee that CRISPR-Cas9 will not provide for undefined, unanticipated effects. There have already been cases in which genome modification resulted in types of cancer. Scientists agree that CRISPR-Cas9 might have adverse effects on human genomes because it is still hard to predict what the effects of a genome modification will be in the long term. For instance, scientists fear that "curing" one disease, could cause another.[44] On the one hand, these unanticipated (direct or indirect) effects occur because of limits in the knowledge of the functioning of human genes. However, on the other hand, they occur because of the reliability of the technology itself.[45] This is because there is a lack of knowledge about what the influence of certain genome modification will entail. Therefore, it remains unclear how specific and reliable the CRISPR-Cas9 technology actually is. Consequently, scientists think that, even if safety and reliability improve, there will still be a possibility that off-target mutations occur. Nonetheless, it shall be noted that part of the scientific community believes that these technical issues will be dealt with over time.[46]

[40] Doudna and Charpentier (n 3).
[41] Baltimore and others (n 5).
[42] Carl Zimmer, 'Breakthrough DNA Editor Born of Bacteria' (*Quanta Magazine*, 2015) <https://www.quantamagazine.org/crispr-natural-history-in-bacteria-20150206>.
[43] Doudna and Charpentier (n 3); Baltimore and others (n 5); Bosley and others (n 5).
[44] Bosley and others (n 5).
[45] Baltimore and others (n 5).
[46] Bosley and others (n 5).

2.3.1 Ethical perspective

The clinical application of CRISPR-Cas9 on humans gives rise to several issues from ethical and social perspectives. As mentioned above, research has shown how much ethic meaning and concepts can diverge based on cultural, social, and geographical location.[47] Nonetheless, an insight into particular ethical and social issues will be given hereafter. In that regard, it is important to know that these ethical and social "frictions: are not new, as most of them were already present prior to the existence of CRISPR-Cas9, especially in the field of genome research and synthetic biology.[48] Mostly, they revolve around the question "Should we play God?", and ethical frictions with regard to altering the human genetic makeup are not new.[49] However, due to the technological developments that CRISPR-Cas9 made, these ethical and social issues became eminently visible (again), and gave life to additional debates in the field.

The ethical debate that surrounds the clinical application of CRISPR-Cas9 on humans focusses on the types of applications and the purposes thereof. As already described above, a distinction in the types of applications can be made in to somatic and germ line applications (see also the figure above). Germ line applications imply that modified cells will convey their information about their "modifications" to the next generation of cells. Hence, there is the possibility that altering the genetic makeup of the cell will be passed on to descendants.[50] Concerning the purposes for types of applications, a distinction can be made between a therapeutical and enhancement purposes (see also the figure above). The therapeutical purpose constitutes genome engineering for the purpose of disease-curing or disease-prevention, whereas the enhancement purpose constitutes genome engineering for the purpose of enhancing (or improving) the human species.[51]

The majority of the scientists in the field of the CRISPR-Cas9 technology stresses the possibility of a "slippery slope" effect. The idea of a "slippery slope" essentially entails that the lines that are drawn between the various types of applications and their purposes will blur (or even fade) over time. This means that the purpose of disease curing (via therapeutical somatic applications) will shift towards less compelling or even undesirable reasons of applications, such as enhancing future generations for futile discriminatory reasons (via enhancement germ line applications).[52] In that regard, the majority of the human genome engineering scientists agree that the human genome is ethical when it is applied solely for diseasing-curing (medical or therapeutical) purposes only, and on current generations of humans (somatic applications).[53] The following reasons are given by scientists to support their views.

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[47] Awad and others (n 22).
[48] Peter Dabrock, 'Playing God? Synthetic Biology as a Theological and Ethical Challenge' (2009) 3 Systems and Synthetic Biology 47.
[49] ibid.
[50] Baltimore and others (n 5).
[51] ibid.
[52] Bosley and others (n 5); Baltimore and others (n 5).
[53] Bosley and others (n 5); Ishii (n 33).

The first and foremost argument relates to the idea that future generations should be allowed self-determination. This means that it should not be the current generation of humans to decide the faith of future generations, as future generations should be autonomous in deciding what is best for them.[54] This is also defined as the "intergenerational equity".[55] "Intergenerational equity" is a concept that aims to strive for fairness and justice between generations. Essentially, it assumes that, when something affects future generations, it does not "belong" to any generation. Rather, it "belongs" to all generations, and requires behaving accordingly.[56] The applicability of the concept of "intergenerational equity" is empowered by the fact that it remains unclear who actually benefits from the modification of the genomes of future generations of humans. If the present generation of humans (e.g. parents) decide that a particular genome should be modified because this would be better for the future generations of humans (e.g. children), would future generation actually benefit from it, or would it only satisfy the present generation?[57]

Another argument, given by Ishii, is that germ line applications are undesirable from an evolutionary perspective, as the modification of the human germ line genome should be considered as a grave interference with human life, as such undesirable.[58] Ishii fears that modification of germ line might change the human species permanently over time, as the long-term consequences of genome modification remain unclear.[59] This would endanger the diversity within the human species.[60] In that regard, a more radical view is taken Moreno, which stresses that the intentional germ line application of CRISPR-Cas9 for enhancement purposes might create "superhumans", as pictured in the movies *Gattaca* (1997) and *The Boys From Brazil* (1978).[61] Additionally, the "global effect of genome modification" can also give rise to other, unexpected effects. As already shown by several researches, *inter alia* one regarding gene modification of mosquitos, modified organisms will eventually crossbreed with non-modified organisms. This means that eventually the non-modified species will be driven out by the modified species.[62] Globalization could cause a similar result with regard to humans. "Gene-edited humans" will travel around the globe and will have children with "non-gene-edited humans". This might cause that ultimately, the entire human species would consist of "gene-edited humans".

On the same topic, another issue was raised by late Stephen Hawking in his posthumous book "Brief Answers to the Big Questions". This is the issue of so-called "unfair warfare".[63]

[54] Bosley and others (n 5); Ishii (n 33).
[55] Brown Weiss Edith, 'Intergenerational Equity', *Sustainable Practices in the Built Environment, Second Edition* (Oxford University Press 2008).
[56] ibid.
[57] Bosley and others (n 5).
[58] Ishii (n 33).
[59] Bosley and others (n 5).
[60] ibid.
[61] ibid.
[62] Caplan and others (n 3).
[63] Hawking (n 1).

Hawking stresses that genome engineering technologies in the future will likely not be used solely for disease-curing purposes in the medical realm, but also in order to advance warfare abilities.[64] In other words, Hawking stresses that some states might modify the genomes of their population in order to have better, stronger, more intelligent, soldiers who could make certain states stronger on the international level. Consequently, this might lead to unfair warfare and, ultimately, might create military superpowers.[65]

2.3.2 Societal perspective

One benefit for society would be that CRISPR-Cas9 is believed to (eventually) have a significant impact in the field of medicine and medical care by providing treatments for certain diseases, which would, according to scientists, improve the quality of life.[66] However, if CRISPR-Cas9 can live up to its medical potential, this would mean that the life expectancy of humans will rise. For the (global) society, this could (or would) put a burden on the consumption of resources, which would pose a significant challenge.[67]

Another issue that has been pointed out concerns the distribution of the possibilities connected to CRISPR-Cas9. Human genome engineering technologies are expensive (even CRISPR-Cas9, even though it is relatively cheaper than others), and therefore might be affordable to rich people. In the light of enhancement germ line applications, this would result in different classes of humans. Consequently, only the wealthy classes would be able to enhance their "kind".[68] Even though CRISPR-Cas9 is a relatively cheap technology to use, it is still not likely that it will be available all around the world, especially in developing countries.

2.3.3 Legal perspective

From a legal perspective, according to scholars, the existing regulatory framework that governs human genome engineering, is not able to regulate the CRISPR-Cas9 technology in a *sufficient* manner.[69] This is the case because existing regulatory frameworks are based on the methodology of conventional genome engineering. The methodology of conventional genome engineering is based on "the use of a drug resistance or marker gene to for a rare desired mutant among a large excess of variants", whereas CRISPR-Cas9 is based on another concept. The CRISPR-Cas9 technology is significantly different from this methodology, due to the way it works (as described in paragraph 2.2 of this chapter), as well as its accessibility (cheapness, effectiveness, and specificity). Scientists stress that it is of utmost importance that legislators need to become aware of its characteristics, because, as they argue, sufficiently understanding the basis of the technology is necessary to facilitate a rational public discourse and necessary

[64] ibid.
[65] ibid.
[66] Bosley and others (n 5).
[67] ibid.
[68] ibid.
[69] Kipling (n 2); Isasi, Kleiderman and Knoppers (n 2); Bosley and others (n 5).

to nurture responsible uses of the CRISPR-Cas9 technology without hindering the development of the technology, as well as the possibilities to use the technology for research.[70]

Moreover, research shows that the regulatory framework is often insufficient from other points of view. In some of the jurisdictions where there is a regulatory framework that governs CRISPR-Cas9, the legal rules are non-binding, as they are closer to guidelines.[71] Research shows as well that in some jurisdictions, the legal rules are ambiguous, and it is not clear which obligations ought to be met.[72] On top of that, some jurisdictions have a very narrow regulatory framework as they only concern Intellectual Property law and ethical standards for research.[73]

One more issue regards the enforcement of legal rules. Some jurisdictions either have a strict ban or mere guidelines.[74] According to scientists, imposing a ban on human genome modification would be ineffective as, since CRISPR-Cas9 is very cheap and accessible, it would be hard to enforce the ban.[75]. Using the withdrawal of research funds as an effective regulatory measure, as done in the past, would not be feasible anymore because it is possible for individuals to purchase the technology without any funds.[76]

Another issue concerns the fact that the availability of CRISPR-Cas9 poses risks, such as lack of safety or quality of the modifications. It is relatively cheap and easy for one to buy a "Do-it-yourself-CRISPR-kit" online and start modifying genes themselves.[77] Moreover, there are already private organizations that started commercializing CRISPR-Cas9. On websites, such as *Synthego*, one could buy modified genomes according to their preferences.[78] Even though those kits do not apply to the human genome yet, both developments raise questions with regard to the safety of these modifications, as there could potentially be no quality check regarding these modifications. Mal-modified cells could ultimately and potentially be harmful to the health and well-being of the human species in the future, should similar kits become available for human genome engineering too.

An additional issue is related to the global legal landscape. Currently, there is no global consensus on how technology should be regulated. Most jurisdictions have different legal rules on genome engineering technologies.[79] As a consequence, this could cause so-called “forum shopping” (or “genome tourism”). The notion of so-called “forum shopping” is one of the

[70] Doudna and Charpentier (n 3).
[71] Ishii (n 33).
[72] Heidi Ledford, ‘The Landscape for Human Genome Editing’ (2015) 526 Nature 310.
[73] Bosley and others (n 5).
[74] Ishii (n 33); Ledford (n 72).
[75] Bosley and others (n 5).
[76] ibid.
[77] ‘Do-It-Yourself CRISPR Kit’ <http://www.the-odin.com/diy-crispr-kit/>; On this website, everyone is able to buy a CRISPR-kit, with which one can modify genes, for around $150,00.
[78] ‘Synthego’ <https://www.synthego.com/>.
[79] Ishii (n 33); Kipling (n 2); Bosley and others (n 5); Baltimore and others (n 5); Baltimore and others (n 14).

reasons to cause the aforementioned.[80] Essentially, "forum shopping" entails that if the legislation of country X allows certain behaviours, whereas the legislation of country Y prohibits particular behaviour, people will choose country X because that jurisdiction is less restrictive. In that regard, it is necessary to instate globally harmonized legislation. Without globally harmonized legislation, this circumstance would lead to "genome tourism". CRISPR-Cas9 becomes a viable way of treating diseases, "genome tourism" might result in patients going the more flexible jurisdictions in order to get treatment. This could lead to risks for safety and health.[81] "Forum shopping" is already an occurring phenomenon in gene-editing livestock research, as scientists, due regulatory confusion as well as a lack of funding, are taking their gene-edited livestock to other countries.[82]

A final issue that should be considered when regulating clinical applications of CRISPR-Cas9 on humans relates to the so-called *Collingridge dilemma*. This theory implies that there is a trade-off between the convenience of influencing and/or controlling the development of technology and knowing the impact of that technology. This trade-off can be divided into two elements, namely an information problem and a power problem. The information problem relates to the fact that impacts of technologies cannot be easily predicted until the technology is extensively developed and widely used, whereas the power problem relates to the fact that control over or change of technology is difficult when the technology has become entrenched.[83] On the one hand, it is desirable to intervene at an early stage in order to avoid another Thalidomide (or Contergan) crisis[84] or prevent Josef Mengele-like practices[85], as well as to cope with the ethical and social frictions deriving from the clinical applications of CRISPR-Cas9 on humans. On the other hand, however, if CRISPR-Cas9 is regulated at a too early stage, it could be possible that the development of the technology is hindered.

[80] Avi Bell, *Libel Tourism: International Forum Shopping for Defamation Claims* (Jerusalem Center for Public Affairs 2008); Forum shopping is a well-known phenomenon in libel cases. In those cases, researched has shown that people were likely to go to jurisdictions in which it has greatest chances of success for their claims to be sustained. This phenomenon is called forum shopping or libel tourism.

[81] Bosley and others (n 5).

[82] Heidi Ledford, 'Gene-Edited Animal Creators Look beyond US Market' (2019) 566 Nature 433.

[83] David Collingridge, *The Social Control of Technology* (Frances Pinter 1980).

[84] CA Heaton, *The Chemical Industry* (Blackie Academic & Professional 1994); Thalidomide was a drug prescribed for pregnant woman in order to treat nausea and morning sickness. After the woman gave birth, children were born with different types malformations. The development led to stricter drug (development) regulation.

[85] Israel Gutman and others, *Anatomy of the Auschwitz Death Camp* (Published in association with the United States Holocaust Memorial Museum, Washington, DC by Indiana University Press 1994); Josef Mengele was a doctor who worked in concentration camp Auschwitz during World War II. In that period, Mengele conducted experiments on inmates, in which he did not consider the health, safety, or physical and emotional suffering of the victims.

3. Legal frameworks governing human genome engineering

In this chapter, the relevant and applicable UN, EU, and CoE legal frameworks regarding human genome engineering will be examined. First of all, a general (global) overview will be provided into the global legal landscape regarding human genome engineering. Subsequently, a detailed analysis of the relevant provisions of the UN, EU, and CoE legal frameworks will be provided. However, only the relevant, when taking into account the perspectives which are mentioned in the previous chapter, provisions will be highlighted. After all relevant provisions are analysed and explained, this chapter will provide the legal rationales that are underlying the legal frameworks.

3.1 Overview of the global legal landscape

As mentioned in the previous chapter, the ethical and legal debate around human genome engineering concerns germ line applications of CRISPR-Cas9, but also other human genome technologies such as ZFNs and TALENs. In that sense, the debate on whether or not germ line modifications should be allowed is not new. Ishii and Araki[86], as well as Isasi, Kleiderman and Knoppers[87], conducted researches into the current legal landscape of several countries with regard to human genome engineering.

3.1.1 Current global legal landscape

The majority of the countries examined by the studies as mentioned above, have banned the modification of germ line cells. Out of the 39 examined countries, 29 countries prohibit the modification of germ line cells. The remaining of the examined countries are ambiguous about what the legal status of germ line modification is. Some of these jurisdictions were more restrictive than others (see Figures 3 and 4).[88] More permissive countries generally have systems in place where a case-by-case approval by the licensor, which is usually a governmental body, is needed. However, this could lead to arbitrary applications and/or inconsistencies. This is to say because the denial or allowance of certain types of applications will be assigned in the absence of clear-cut requirements, as a case-by-case approach allows for different requirements to be applicable. Hence, there is great legal uncertainty for the (potential) licensee.[89]

Moreover, some countries that ban germ line modification have chosen to implement guidelines in order to impose this ban, which are harder to enforce since they provide merely guidance rather than strict binding provisions (also see Figure 3 and 4).[90] Most countries that

[86] Tetsuya Ishii and Motoko Araki, 'International Regulatory Landscape and Integration of Corrective Genome Editing into in Vitro Fertilization' (2014) 12 Reproductive Biology and Endocrinology 108.

[87] Isasi, Kleiderman and Knoppers (n 2); With regard to the data provided in this research, it is important to note these data are the most recent data. Moreover, there is no data available concerning that countries that are not examined by this research. Hence, it is not possible to make a comparison to these countries.

[88] Ishii and Araki (n 86); Isasi, Kleiderman and Knoppers (n 2).

[89] Ishii and Araki (n 86); Isasi, Kleiderman and Knoppers (n 2).

[90] Ishii and Araki (n 86); Isasi, Kleiderman and Knoppers (n 2).

ban germ line modifications accompanied the ban with criminal sanctions.[91] Nonetheless, it appears that in most jurisdictions the ban is not absolute, meaning that there are (limited) exceptions which allow for germ line modifications. For example, in Belgium, Germany and France there is legislation in place that provides for an exception for applications that are therapeutically beneficial to an embryo, that is necessary for the preservation of the embryo's life, or that are needed in order to achieve pregnancy.[92] However, it appears that some countries have legal provisions that consist of vague language, which makes them open to multiple interpretations.[93]

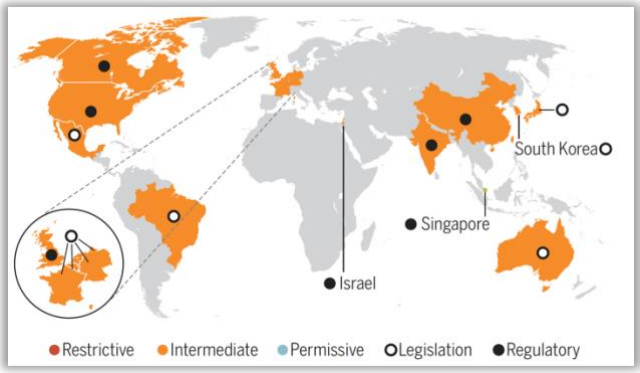

Figure 3 – Legislation of countries regarding human somatic gene modification (Isasi et al, 2016)

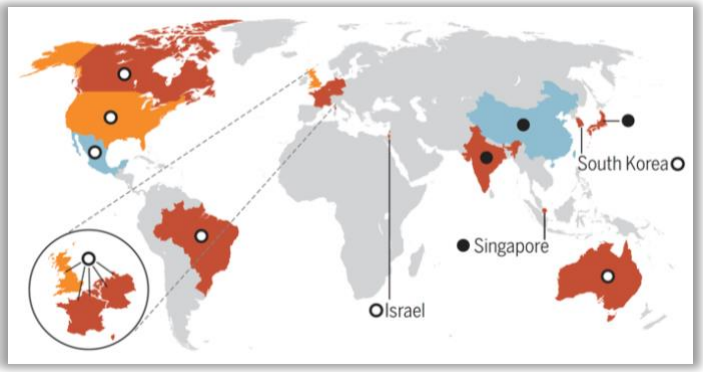

Figure 4 – Legislation of countries regarding human germ line modification (Isasi et al, 2016)

3.1.2 Focus of the current global legal landscape

Most of the countries that ban germ line modifications tend to take a "product-based" and/or "process-based" approach, much like the existing Genetic Modified Organisms (GMOs) legislation. A product-based approach means that countries regulate (or ban) products, such as modified germlines, whereas a process-based approach means that countries regulate (or ban) processes, such as types of technologies (e.g. ZFNs and TALENs).[94] The legal regimes do not take "purpose-based" approach, meaning that countries regulate (or ban) a specific purpose, such as therapeutical or enhancement, and reproductive or scientific. In other words, legal regimes focus on the regulation of trial, rather than of actual applications.[95]

3.2 Relevant and applicable rationales underlying the legal frameworks

On a global level, the United Nations have adopted two of conventions relevant for this research. In 1997, at a conference of the United Nations Education, Scientific and Cultural Organization (UNESCO), the UNESCO Universal Declaration on Bioethics and Human Rights (also referred to as UDBHR), which was revised in 2005, and the UNESCO Universal Declaration on the Human Genome and Human Rights (also referred to as UDHGHR) were

[91] Isasi, Kleiderman and Knoppers (n 2).
[92] ibid; Ishii and Araki (n 86).
[93] Isasi, Kleiderman and Knoppers (n 2).
[94] ibid.
[95] ibid.

adopted.[96] The Declaration on Bioethics and Human Rights aims to address general bioethical issues, whereas the Declaration on the Human Genome and Human Rights aims to address specific bioethical issues, namely issues regarding the human genome. Even though non-binding, the UN hopes (and anticipates) that both instruments will eventually become binding through use and application, like the Universal Declaration of Human Rights.[97]

In this paragraph, the legal rationales that underlie the current legal landscape regarding the clinical application (or use) of human genome engineering technologies are described and analysed. Hereunder, in Figure 5, an overview is provided on which rationale can be considered as an underlying rationale for what legislation.[98]

	UDBHR	**UDHGHR**	***Oviedo Convention***
Human Dignity and Autonomy	Articles 2 and 3	Preamble Articles 11 and 24	Preamble Article 5
Intergenerational Equity	Article 16	Absent	Article 13
Sex Selection	Implicit	Implicit	Article 14
Justice and Equality	Article 10	Absent	Absent
Benefit and Harm	Article 4	Implicit	Implicit

Figure 5 – Overview of underlying rationales per piece of legislation

Surprisingly, the precautionary principle seems not to be a rationale underlying the UNESCO Universal Declaration on Bioethics and Human Rights and UNESCO Universal Declaration on the Human Genome and Human Rights, as well as the *Oviedo Convention*. The precautionary principle entails that risks should be reduced in the case where there is (still) scientific uncertainty. In other words, the causal link between the risk and a particular consequence is not (yet) established.[99] The precautionary principle is process-based, rather than outcome-based. It applies if there are reasonable grounds for concern that the potentially dangerous effects on the, in this case, human (species) and/or health may be inconsistent with a high level of protection chosen.[100] Neither piece of legislation holds a clear reference to this

[96] Ten Have and Gordijn (n 26); Roberto Andorno, 'Biomedicine and International Human Rights Law: In Search of a Global Consensus' (2002) 80 Bulletin of the World Health Organization 959.

[97] Ten Have and Gordijn (n 26); Roberto Andorno, 'Global Bioethics at UNESCO: In Defence of the Universal Declaration on Bioethics and Human Rights' (2007) 33 Journal of Medical Ethics 150.

[98] The definitions of the rationales as are mentioned in the overview in Figure 5 are based upon a combination of, on the one hand, the definition that the piece of legislation has attributed to the rationale, and, on the other hand, what the rationale, in essence, aims to protect or strives for.

[99] Roberto Andorno, 'The Precautionary Principle: A New Legal Standard for a Technological Age' (2004) 1 Journal of International Biotechnology Law 11; Marco Martuzzi and Joel A Tickner, *The Precautionary Principle: Protecting Public Health, the Environment and the Future of Our Children* (2004).

[100] Andorno, 'The Precautionary Principle: A New Legal Standard for a Technological Age' (n 99); Martuzzi and Tickner (n 99).

principle. Concerning the UDBHR, the precautionary principle was removed from the final version of the UDBHR. The legislator consciously decided to remove the precautionary principle from the document.[101]

3.2.1 UNESCO Universal Declaration on Bioethics and Human Rights

The UNESCO Universal Declaration on Bioethics and Human Rights consists of very general principles. The UNESCO has chosen to do so because, according to it, it would otherwise be nearly impossible to reach a consensus on these highly sensitive topics. In other words, the Declaration tries to establish universally accepted bioethical norms with respect to cultural diversity.[102]

Through the UDBHR, the UN aims to set minimum global standards regarding bioethics, which are agreeable to all participating countries, while recognizing the cultural and religious sensitivity of bioethics.[103] This means that countries are allowed to adopt stricter rules, but they should at least provide the same level of protection as the UDBHR.[104]As mentioned above, the UDBHR provides for several principles regarding bioethics. The principles that are relevant for this research will be analysed hereafter.

The first relevant principle is the principle to protect human dignity and human rights (Article 2 and 3). Article 2 of the UDBHR[105] says, the aim of the declaration is to promote and respect human dignity. Article 3 of the UDBHR[106], emphasizes this aim. This principle aims to protect human dignity, but the Declaration omits to define what the notion of human dignity entails.[107] Some scholars claim that 'human dignity' is a synonym for 'respect for autonomy' and that it, therefore, could be abandoned without it being detrimental.[108] However, the notion of human dignity concerns more than 'respect for autonomy' and cannot be defined in clear and

[101] Andorno, 'Global Bioethics at UNESCO: In Defence of the Universal Declaration on Bioethics and Human Rights' (n 97).

[102] Ten Have and Gordijn (n 26); Henk AMJ Ten Have and Michèle S Jean, *The UNESCO Declaration on Bioethics and Human Rights - Background, Principles and Application* (UNESCO 2009); Andorno, 'Global Bioethics at UNESCO: In Defence of the Universal Declaration on Bioethics and Human Rights' (n 97).

[103] William M Sullivan and Will Kymlicka, *The Globalization of Ethics: Religious and Secular Perspectives* (William M Sullivan and Will Kymlicka eds, Cambridge University Press 2007).

[104] ibid.

[105] Article 2 UDBHR (Aims): The aims of this Declaration are:… …(c) to promote respect for human dignity and protect human rights, by ensuring respect for the life of human beings, and fundamental freedoms, consistent with international human rights law… and …(d) to recognize the importance of freedom of scientific research and the benefits derived from scientific and technological developments, while stressing the need for such research and developments to occur within the framework of ethical principles set out in this Declaration and to respect human dignity, human rights and fundamental freedoms;…

[106] Article 3 UDBHR (Human dignity and human rights): "1. Human dignity, human rights and fundamental freedoms are to be fully respected. 2. The interests and welfare of the individual should have priority over the sole interest of science or society."

[107] Roberto Andorno, 'Human Dignity and Human Rights' in UNESCO (ed), *The UNESCO Declaration on Bioethics and Human Rights - Background, principles and application* (2009).

[108] R Macklin, 'Dignity Is a Useless Concept' (2003) 327 BMJ 1419.

unambiguous terms.[109] Human dignity aims to protect the intrinsic value of every human being in a way which is equal to all humans. Essentially, it means that all humans deserve unconditional respect without any form of discrimination.[110] The notion of human dignity can be split up into an "individual" and "collective" element.[111] The "individual" element entails that each human being has certain rights and freedoms, which are not absolute and can be reasonably be limited in a democratic society.[112] The "collective" element entails that humankind or humanity as such has an inherent value.

For a large part, the current notion of human dignity is substantiated on the theory of philosopher Immanuel Kant, which is also referred to as *Kantianism*.[113] According to *Kantianism*, the intrinsic value that a human being has, is derived from the human capacity for "autonomous self-regulation under the categorical imperative".[114] Kant emphasizes the freedom that human beings have the ability to perceive and accept moral laws, which is an ability solely restricted to humans, and this is what human dignity justifies.[115] The categorical imperative is a formal concept which guides the so-called "moral laws". It implies that it should represent certain actions which are rationally required by their nature, but without reference to any further end or goal.[116] Hence, the categorical imperative is a mere formal concept. According to Kant, there is only one categorical imperative conceivable, namely: "Act only in accordance with that maxim through which you can at the same time will that it become a universal law".[117] In other words, behaviour is merely moral when it will universally be considered moral. Another categorical imperative, according to Kant, is: "So act that you use humanity, whether in your own person or in the person of any other, always at the same time as an end, never merely as a means". This imperative entails that humans always have to be treated as an end and never merely as a means to an end.[118] In other words, humans ought not to be instrumentalised in cases where it will not benefit themselves. These are all elements that are instrumental to the current interpretation of the notion of human dignity.[119] Hence, it requires that human integrity and identity ought to be protected from misuse of (bio)technological development (i.e. misuse of the CRISPR-Cas9 technology).[120]

[109] Andorno, 'Human Dignity and Human Rights' (n 107).
[110] ibid.
[111] Dieter Birnbacher, 'Ambiguities in the Concept of Menschenwürde' in Kurt Bayertz (ed), *Sanctity of Life and Human Dignity* (Springer, Dordrecht 1996); Roberto Andorno, 'Dignity of the Person in the Light of International Biomedical Law' (2005) 1 Medicina e Morale 91.
[112] Birnbacher (n 111); Andorno, 'Dignity of the Person in the Light of International Biomedical Law' (n 111).
[113] Andorno, 'Human Dignity and Human Rights' (n 107); Immanuel Kant, 'Groundwork of the Metaphysics of Morals' in Immanuel Kant (ed), *Practical Philosophy* (Cambridge University Press 1996).
[114] Kant (n 113).
[115] ibid.
[116] ibid.
[117] ibid.
[118] ibid.
[119] Andorno, 'Human Dignity and Human Rights' (n 107).
[120] Birnbacher (n 111); Andorno, 'Dignity of the Person in the Light of International Biomedical Law' (n 111).

Moreover, Immanuel Kant claims that human autonomy is a key feature of human dignity.[121] The embodiment of the respect for human autonomy is the principle to protect the autonomy of the human subject (Article 5).[122] The principle to protect human autonomy can already be found in the UNESCO Universal Declaration on Human Rights (hereafter: UDHR), which is the classical expression of human rights.[123] It serves as a fundamental principle upon which a plethora of provisions of the UDHR[124] are based. The UDHR, on its parts, derives the principle to protect human autonomy from the Nuremberg Code.[125] This Code was established almost right after World War II, because medical researchers were accused of committing crimes against humanity by performing certain types of trials on camp prisoners in the name of medical research, without obtaining the patient's consent.[126] The Code, as well as the UDHR and UDBHR, aim to prevent and abolish these types of practices.[127] In order to do so, they strive to protect and respect human autonomy. In essence, the principle of autonomy, which can be divided into "autos" (self) and "nomos" (rule), attributes the right to a human individual to self-determine.[128] More concretely, the notion of respecting human autonomy entails that medical practitioners must respect the individual's ability to make informed decisions about personal matters (i.e. medical treatment).[129]

The second relevant principle is the principle to increase benefit and reduce harm (Article 4).[130] The principle to increase benefit and reduce harm follows logically and incontrovertibly from Article 3 of the Declaration (i.e. the principle to protect human dignity and human rights).[131] As mentioned above, the notion of human dignity assumes that humanity possesses a certain

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[121] Kant (n 113).

[122] Article 5 UDBHR (Autonomy and individual responsibility): "The autonomy of persons to make decisions, while taking responsibility for those decisions and respecting the autonomy of others, is to be respected. For persons who are not capable of exercising autonomy, special measures are to be taken to protect their rights and interests."

[123] Andorno, 'Human Dignity and Human Rights' (n 107).

[124] The principle to protect human dignity serves as an underlying basis for several other ratios in the UDHR, such liberty (Article 3), freedom from slavery (Article 4), freedom from torture and degrading punishment (Article 5), protection from arbitrary arrest (Article 9), freedom from arbitrary interference (Article 12), freedom of movement (Article 13), seek asylum (Article 14), marry voluntarily and found a family (Article 16), own property (Article 17), freedom of thought, opinion and expression (Articles 18 and 19), freedom of peaceful assembly (Article 20), take part in government (Article 21), work (Article 23), choice of education (Articles 26), and participation in the cultural life of a community (Article 27).

[125] Andorno, 'Human Dignity and Human Rights' (n 107).

[126] George J Annas and Michael A Grodin, *The Nazi Doctors and the Nuremberg Code: Human Rights in Human Experimentation* (Oxford University Press 1992).

[127] Ten Have and Gordijn (n 26); Andorno, 'Human Dignity and Human Rights' (n 107).

[128] Antoine Baumann and others, 'Elective Non-Therapeutic Intensive Care and the Four Principles of Medical Ethics' (2013) 39 Journal of Medical Ethics 139; Jonathan F Will, 'A Brief Historical and Theoretical Perspective on Patient Autonomy and Medical Decision Making: Part II: The Autonomy Model' 1491.

[129] Baumann and others (n 128); Will (n 128).

[130] Article 4 UDBHR (Benefit and harm): "In applying and advancing scientific knowledge, medical practice and associated technologies, direct and indirect benefits to patients, research participants and other affected individuals should be maximized, and any possible harm to such individuals should be minimized."

[131] Edmund D Pellegrino, 'Benefit and Harm' in UNESCO (ed), *The UNESCO Declaration on Bioethics and Human Rights - Background, principles and application* (2009).

inherent value which needs to be protected. The principles of beneficence and non-maleficence aim to fulfil this obligation. [132] The assessment of these principles requires a case-by-case approach and consists of a balancing exercise in which the benefits should outweigh the harms.[133] In order to perform this balancing exercise, judgments ought to be made on the basis of benefits, harms, and risks.[134]

The balancing exercise requires that an estimation is made of the probability and projections of the expected impact on the individual human and society as such, regarding the clinical applications of (bio)technologies, such as CRISPR-Cas9.[135] Examples of benefits are advancing the individual and or societal interests and producing new knowledge which could be beneficial for future individuals. Moreover, examples of sorts of risks are the probability (or probabilities) of harming the interests of the human individual or social order. Finally, examples of harm could be financial, physical, emotional, and/or spiritual, either alone or in combination.[136] One (and the most used) method to assess this balancing exercise, is the so-called "QALYs-method".[137] QALYs is an acronym and stands for *quality-adjusted life years*. Its tenor is to make "cost-benefit analysis", as it quantifies the cost/utility ratio for either clinical decisions made in the case of a human individual as well as decisions made in the determination of a public (health)policy. This method aims to find a balance between the quality and length of life. The utility of the outcome is measured by assessing the number of years that the human individual is anticipated to live and the quality of those years.[138] However, some significant issues arise concerning the ethical correctness of the QALYs-method. This is to say because this method is substantiated on the ethical theory of *utilitarianism*. *Utilitarianism* is a variant of the theory of *consequentialism*, and it aims to promote actions which maximize the happiness and eudaimonia of the majority. Essentially, it attempts to maximize the net positive pleasure.[139] In that regard, the main critique of the QALYs-method is that human life cannot be quantified per se, even though the QALYs-method seeks to do so.[140]

Even though this principle to increase harm and reduce harm are not explicitly mentioned in neither the UDHGHR nor the *Oviedo Convention*, it could be considered that this principle is nonetheless a rationale which underlies the UDHGHR and the *Oviedo Convention*. This is to say because, as mentioned above, the notion of human dignity assumes that humans possess a certain inherent value which needs to be protected. One might say that the concept of human dignity requires the increasing of benefits and the reducing of harms in order to adhere to the

[132] Tom L Beauchamp and James F Childress, *Principles of Biomedical Ethics* (Oxford University Press 2001).
[133] ibid.
[134] ibid.
[135] ibid.
[136] ibid.
[137] Alan Williams, 'Economics, QALYs and Medical Ethics — A Health Economist's Perspective' (1995) 3 Health Care Analysis 221.
[138] ibid.
[139] John Stuart Mill, *Utilitarianism* (Parker, Son & Bourn, West Strand 1863).
[140] Pellegrino (n 131).

inherent value that humans possess. As will be mentioned further on in this thesis, the concept of human dignity is a rationale that underlies the UDHGHR and the *Oviedo Convention*.

The third relevant principle is the principle to promote equality, justice and equity (Article 10).[141] This principle can be divided into three separate concepts, namely 'equality', 'justice' and 'equity'. The notion of justice is the foundation of this principle and should be interpreted according to the theories of Aristotle and Rawls.[142] According to Aristotle, justice is giving each individual what is appropriate for it to receive. In other words, there would be injustice when persons who are equal do not receive equal portions and vice versa.[143] Aristotle's notion of justice gives no definition or criterion of what is appropriate but provides two categories of justice: corrective or commutative justice and distributive justice.[144] Discussing corrective or commutative justice goes beyond the scope of this thesis and, therefore, only the concept of distributive justice will be discussed.[145] The concept of distributive justice, as posed by Aristotle, establishes that the "distributions of fees, wealth, and the other things that are divided among the members of the body politic". In other words, every individual ought to be rewarded in proportion to its merits.[146]

However, the current notion of distributive justice has slightly changed with regard to the notion that Aristotle introduced.[147] The current concept of distributive justice is based on the theory of Rawls and describes how society should allocate resources to individuals that have conflicting interests, without considering the merits of the individuals. According to Rawls, "each person is to have an equal right to the most extensive total system of equal basic liberties compatible with a similar system of liberty for all".[148] Rawls proposes the principle of fair equality of opportunities and that all social significances[149] ought to be distributed equally.[150] Moreover, Rawls argues that, in the case of unequal distribution of resources, unequal distribution is only accepted if it would favour all members within the society or the ones who would need the resources the most.[151] The concept of distributive becomes increasingly important in the case where there is a scarcity of resources.[152] According to Callahan, the

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[141] Article 10 UDBHR (Equality, justice and equity): "The fundamental equality of all human beings in dignity and rights is to be respected so that they are treated justly and equitably."

[142] Maria Patrão Neves, 'Respect for Human Vulnerability and Personal Integrity' in UNESCO (ed), *The UNESCO Declaration on Bioethics and Human Rights - Background, principles and application* (2009).

[143] Aristotle, *The Nicomachean Ethics* (Barnes and Noble 2004).

[144] ibid.

[145] The concept of corrective or commutative justice regards 'private transactions. This type of justice requires that, in case of damages, those wrongdoers pay damages to victims, which corresponds to the extent of the harm which has been done. The notion is not relevant for this thesis and will therefore not be discussed.

[146] Aristotle (n 143).

[147] Samuel Fleischacker, *A Short History of Distributive Justice* (Harvard University Press 2004).

[148] John Rawls, *A Theory of Justice* (Revised Ed, Harvard University Press 1999).

[149] "Social values", according to Rawls, are liberties, opportunities, wealth, social bases and self-respect.

[150] Rawls (n 148).

[151] ibid.

[152] Daniel Callahan, 'Equity, Quality, and Patient Rights: Can They Be Reconciled?' in Fernando S Lolas and Lorenzo C Agar (eds), *Interfaces between bioethics and the empirical social sciences* (World Health Organization 2002).

meaning of this concept is highlighted in cases in which swift technological developments could constrain the fair use of a particular technology, especially when biotechnology should be considered as a scarce resource.[153] This is most certainly the case for the CRISPR-Cas9, as it could be possible that the technology will only be available to certain 'classes' within society.

The other elements that complement the element of 'justice' in this principle are 'equity' and 'equality'. The element of 'equity' should once more be interpreted according to the theories of Aristotle and Rawls.[154] According to both, essentially, equity is fundamental to justice and can be considered as justice.[155] Moreover, according to Rawls, equity merely occurs when all individuals are free to define and accept the rules, benefits and charges. If there is any divergence in benefits or charges, there is only equity if it benefits all individuals.[156] The notion of equity, together with justice, serves as the basis for equality. As enshrined in Article 10 of the UDBHR, human individuals should be considered equal in dignity, justice, rights, opportunities, freedom, benefits, and obligations, and justice and equity are only to be achieved if human individuals are treated equally in that regard.[157]

The fourth and final relevant principle is the principle to protect future generations (Article 16).[158] This principle aims to prevent decisions made by the present generations that will adversely affect future generations. Essentially, this principle signifies that, when making decisions, one should not only consider ourselves (i.e. the present generation) but also the global community and the future generation humans.[159] The inclusion of this principle in the UDBHR implies that the concept of intergenerational justice or intergenerational equity, which was already present in environmental ethics, is taken into account with regard to bioethics as well.[160] This principle aims to protect the future of humanity. This is to say because 'humanity' does not merely consist of the humans living today, but it also consists of future generations.[161] This principle will be particularly relevant when decisions need to be made with regard to swift technological developments that might contribute to the improvement of human lives through new therapies[162], which is the case for the CRISPR-Cas9 technology. Nonetheless, it could be the case that through applications of these technologies, undesired conditions for future generations will occur. Hence, the decision-making process should, with regard to this kind of

[153] ibid.
[154] Neves (n 142).
[155] Aristotle (n 143); Rawls (n 148).
[156] Rawls (n 148).
[157] Neves (n 142).
[158] Article 16 UDBHR (Protecting future generations): "The impact of life sciences on future generations, including on their genetic constitution, should be given due regard."
[159] Takayuki Morisaki, 'Protecting Future Generations' in UNESCO (ed), *The UNESCO Declaration on Bioethics and Human Rights - Background, principles and application* (2009).
[160] Emmanuel Agius, 'Environmental Ethics: Towards an Intergenerational Perspective' in Henk AMJ Ten Have (ed), *Environmental Ethics and International Policy* (UNESCO 2006).
[161] ibid.
[162] Morisaki (n 159).

issues, take into account the impact of a technology on present and future generations humans.[163]

3.2.2 UNESCO Universal Declaration on the Human Genome and Human Rights

The other Declaration that the UNESCO has adopted is the UNESCO Universal Declaration on the Human Genome and Human Rights, which regards a more specific topic, namely the human genome. Content-wise, the UDHGHR is very similar to the UDBHR, as both declarations address the interplay between bioethics and human rights.[164] The UDBHR provides for a codification and promotion of bioethical norm on a global level, even though it is non-binding, whereas the UDHGHR signifies that the human genome is part of the common heritage humanity (Article 1)[165] and prohibits practices which are contrary to human dignity.[166] Like the UDBHR, a fundamental principle for the UDHGHR is the principle to promote and respect human dignity. This is to say because of the preamble of the Declaration[167] and two provisions, namely Article 11 and 24, emphasize this principle. These provisions are particularly relevant for this thesis, as they emphasize the importance of the principle to promote and respect human dignity with regard to the human genome in particular.

Article 11 of the UDHGHR[168] prohibits practices which are deemed a contrary to human dignity. The same definition of human dignity applies as under the UDBHR.[169] This means that for the UDHGHR, the notion of human dignity entails that it aims to protect the intrinsic value of every human being in a way which is equal to all humans. Essentially, it means that all humans deserve unconditional respect without any form of discrimination.[170] Moreover, Article 24 of the UDHGHR[171] provides for a ban on human germ line modifications, when

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[163] ibid.

[164] Herman Nys, 'Towards an International Treaty on Human Rights and Biomedicine? Some Reflections Inspired by UNESCO's Universal Declaration on Bioethics and Human Rights.' (2006) 13 European Journal of Health Law 5; Andorno, 'Biomedicine and International Human Rights Law: In Search of a Global Consensus' (n 96).

[165] Article 1 UDHGHR: "The human genome underlies the fundamental unity of all members of the human family, as well as the recognition of their inherent dignity and diversity. In a symbolic sense, it is the heritage of humanity."

[166] Ten Have and Gordijn (n 26).

[167] Preamble UDHGHR: The General Conference,… Recognizing that research on the human genome and the resulting applications open up vast prospects for progress in improving the health of individuals and of humankind as a whole, but emphasizing that such research should fully respect human dignity, freedom and human rights, as well as the prohibition of all forms of discrimination based on genetic characteristics…

[168] Article 11 UDHGHR: "Practices which are contrary to human dignity, such as reproductive cloning of human beings, shall not be permitted. States and competent international organizations are invited to co-operate in identifying such practices and in taking, at national or international level, the measures necessary to ensure that the principles set out in this Declaration are respected."

[169] Ten Have and Gordijn (n 26).

[170] ibid.

[171] Article 24 UDHGHR: "The International Bioethics Committee of UNESCO should contribute to the dissemination of the principles set out in this Declaration and to the further examination of issues raised by their applications and by the evolution of the technologies in question. It should organize appropriate consultations with parties concerned, such as vulnerable groups. It should make recommendations, in accordance with UNESCO's statutory procedures, addressed to the General Conference and give advice concerning the follow-up

contrary to human dignity.[172] The provision imposes a ban which is quite similar to Article 13 of the *Oviedo Convention*, which will be elaborated further on in this chapter.[173] On the same topic, the International Bioethics Committee (IBC) of the UN[174] also calls for a moratorium because of specific issues concerning germ line modifications.[175]

3.2.3 European Union legal frameworks

Regarding the EU legal frameworks, the research of Kipling[176] more or less confirms what the researches of Ishii and Araki[177] and Isasi[178] already have shown. Within the European Union there is no legislation in place that governs genetics in general. The European Union currently only holds legislation that regulates agriculture, food and consumer products that contain GMOs.[179] In addition, Kipling's research shows that in the absence of EU legislation regarding general genetics, most Member States have signed the so-called *Oviedo Convention*, which does cover general genetics. The *Oviedo Convention* is an instrument of the Council of Europe, and an account of this convention will be given further on in this paragraph.

The European Union currently only regulates research and clinical trials regarding human genome engineering.[180] At this moment, there is no EU legislation dealing with the clinical application or use of human genome engineering (technologies). It has been left up to the Member States of the EU to decide how to regulate clinical applications (or use) of human genome engineering technologies. Some countries have a more restrictive legal framework in place, whereas other countries have a more permissive legal framework. Some countries allow for certain types of researches, which are mainly various types embryo researches, whereas

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of this Declaration, in particular regarding the identification of practices that could be contrary to human dignity, such as germ-line interventions."

[172] Ten Have and Gordijn (n 26).

[173] Andorno, 'Biomedicine and International Human Rights Law: In Search of a Global Consensus' (n 96); Kipling (n 2).

[174] UNESCO, 'International Bioethics Committee | United Nations Educational, Scientific and Cultural Organization' (*UNESCO*, 2013) <http://www.unesco.org/new/en/social-and-human-sciences/themes/bioethics/international-bioethics-committee/> accessed 26 March 2019; The International Bioethics Committee (IBC) is a body of the United Nations. It was created in 1993 by Dr. Frederico Mayor Zaragoza, the General Director of UNESCO. The IBC consists of 36 independent experts that focuses on life sciences and its applications. The goal of the IBC is ensuring respect for human dignity and freedom. The IBC's tasks tare developing norms of bioethics. These norms are considered soft law (non-binding), nonetheless, they are considered as authoritative in shaping debate and consultations regarding research ethics committees and health policies.

[175] UNESCO, 'UNESCO Panel of Experts Calls for Ban on "Editing" of Human DNA to Avoid Unethical Tampering with Hereditary Traits' (*UNESCO*, 2015) <https://en.unesco.org/news/unesco-panel-experts-calls-ban-editing-human-dna-avoid-unethical-tampering-hereditary-traits?language=en%00> accessed 26 March 2019.

[176] Kipling (n 2).

[177] Ishii and Araki (n 86).

[178] Isasi, Kleiderman and Knoppers (n 2).

[179] Kipling (n 2); Angers and others (n 20).

[180] Kipling (n 2); Angers and others (n 20).

other prohibit such prohibit those researches.[181] Most Member States seem to ban modifications to human germ line cells. However, there seems to be no absolute ban, as most Member States do have various specific exceptions. Some countries have a licensing system in place where a case-by-case approval by the licensor, which makes it possible to be exempted from the ban.[182] In that light, most countries focus their legal framework on regulating IVF, embryo research, or clinical research and trials in general.[183] Notwithstanding, there is a certain degree of consistency in the legislation of Member State regarding the regulation of modifications to human somatic cells. For instance, the United Kingdom, France, Switzerland, Czech Republic, Lithuania, Spain, Greece, Sweden, Estonia and Norway, all allow for modifications to human somatic cells, provided that certain requirements are met, such as obtaining the approval of an ethical review board.[184]

3.2.4 The *Oviedo Convention*

In 1997, the Council of Europe adopted the Convention on Human Rights and Biomedicine[185], otherwise known as the *Oviedo Convention*. The Convention is the first multilateral binding treaty entirely dedicated to addressing human rights issues arising from bioethics.[186] As already mentioned in the previous paragraph, most of the EU Member States have signed the *Oviedo Convention*. Overall, thirty-five States have signed the *Oviedo Convention*. However, only twenty-nine of these States have actually ratified the Convention. Of the States that have actually ratified the *Oviedo Convention*, six have made reservations to the extent to which certain provisions of the Convention are binding. Croatia, Denmark, France, Norway, Switzerland and Turkey all made their respective reservations in order to take a more permissive or restrictive approach.[187]Among the EU Member States not participating in the *Oviedo Convention* some important names appear, such as the United Kingdom and Germany.[188]

As anticipated, the *Oviedo Convention* is a binding legal instrument. This means that if a country has ratified the Convention, it is obliged to adapt its national laws to the Convention.[189] Moreover, the scope of the Convention is the whole domain of human bioethics, which

[181] Kipling (n 2); Angers and others (n 20).
[182] Kipling (n 2); Angers and others (n 20).
[183] Kipling (n 2); Angers and others (n 20).
[184] Kipling (n 2).
[185] Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine.
[186] Roberto Andorno, 'The Oviedo Convention: A European Legal Framework at the Intersection of Human Rights and Health Law' (2006) 2 Journal of International Biotechnology Law 133.
[187] Kipling (n 2).
[188] ibid.
[189] Andorno, 'The Oviedo Convention: A European Legal Framework at the Intersection of Human Rights and Health Law' (n 186); Laurence Lwoff, 'Convention on Human Rights and Biomedicine: The Oviedo Convention' in Ingrid Brena Sesma and Manuel H Ruiz de Chávez (eds), *Bioética y derechos humanos. México y la Convención para la Protección de los Derechos Humanos y la Dignidad del Ser Humano con Respecto de las Aplicaciones de la Biología y la Medicina* (UNAM 1997).

encompasses genetics as well.[190] Consequently, the Convention should be seen as a framework instrument: its broad, general principles should be developed in the years to come through additional protocols on specific issues.[191] The Convention should also be seen as a minimum for common standards. This means that participating countries may implement provisions that impose higher standards, but they may not impose lower standards than the Convention provides for.[192] Furthermore, the Convention needs to be implemented in the national laws of the participating countries.[193]. Another characteristic of the Convention is that judicial protection is left to the national courts. According to Articles 23 and 29 of the Convention, national courts are competent to provide judicial protection but can ask for an advisory opinion of the ECtHR.[194] Finally, another characteristic of the Convention is that the rights that the Convention provides are so-called relative rights. This means that if a country wants to curtail a right provided by the Convention, the same regime applies as to the ECHR.[195] This regime affirms that a right can merely be curtailed insofar it is "prescribed by law and are necessary in a democratic society in the interest of public safety, for the prevention of crime, for the protection of public health or for the protection of the rights and freedoms of others" (Article 26 *Oviedo Convention* in conjunction with Article 8 ECHR). On top of that, in order to prevent arbitrary use of power, the restriction, shall be proportionate to a legitimate aim.[196]

As mentioned above, the *Oviedo Convention* addresses human bioethics. This notion encompasses general human genetics. Hereafter, the relevant articles of the *Oviedo Convention* will be analysed. First of all, the Convention clearly tries to protect the notion of human dignity, as it is referred in the official name of the Convention, its preamble and several provisions (Chapter I – Articles 1 to 4). For example, Article 1 of the Convention[197] explicitly states that it aims to protect human dignity.[198] Another example can be found in Article 3 of the Convention.[199] In this article, another reference to the protection of human dignity can be found as it requires states to take adequate measures to ensure "*equitable access to health of appropriate quality*". Even though this article seems to relate more to the "right to health care", it also refers human dignity as it aims to ensure that persons enjoy the "*highest attainable*

[190] Andorno, 'The Oviedo Convention: A European Legal Framework at the Intersection of Human Rights and Health Law' (n 186).
[191] ibid; Lwoff (n 189).
[192] Andorno, 'The Oviedo Convention: A European Legal Framework at the Intersection of Human Rights and Health Law' (n 186).
[193] ibid.
[194] ibid.
[195] ibid.
[196] ibid.
[197] Article 1 Oviedo Convention (Purpose and object): "Parties to this Convention shall protect the dignity and identity of all human beings and guarantee everyone, without discrimination, respect for their integrity and other rights and fundamental freedoms with regard to the application of biology and medicine. Each Party shall take in its internal law the necessary measures to give effect to the provisions of this Convention."
[198] Andorno, 'The Oviedo Convention: A European Legal Framework at the Intersection of Human Rights and Health Law' (n 186).
[199] Article 3 Oviedo Convention (Equitable access to health care): "Parties, taking into account health needs and available resources, shall take appropriate measures with a view to providing, within their jurisdiction, equitable access to health care of appropriate quality."

standard of physical and mental health".[200] The notion of human dignity is interpreted in line with the interpretation provided by the UDBHR and the UDHGHR.[201]

Moreover, autonomy plays a key role in the *Oviedo Convention*. The preamble[202] of the *Oviedo Convention* emphasizes the importance of human dignity, whereof human autonomy is part, by stating that States should take measures to safeguard human dignity. Moreover, Article 5 of the *Oviedo Convention*[203] is the embodiment of the notion of autonomy. This provision requires that free and informed consent has been given by the person concerned. The notion of autonomy of the *Oviedo Convention* is the same as in the UDBHR.[204] The concept of human autonomy entails that medical practitioners must respect a human individual's ability to make (informed) decisions about personal matters (i.e. medical treatment).[205]

Intergenerational equity and sex selection

Another important issue that is covered by the *Oviedo Convention* is the prohibition of certain types of genetic manipulation practices (Chapter IV – Articles 11 to 14). Articles 13[206] and 14[207], in particular, appear relevant for the purpose of this thesis. Article 13 puts a prohibition on human germ line modifications, and it limits the use of somatic gene modifications to merely preventive, diagnostic and therapeutic applications.[208] This is particularly relevant for the CRISPR-Cas9 technology, as it allows for germ line modifications.

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[200] Andorno, 'The Oviedo Convention: A European Legal Framework at the Intersection of Human Rights and Health Law' (n 186).

[201] The preamble of the Oviedo Convention states that the States of the Council of Europe "[Bear] in mind the Universal Declaration of Human Rights proclaimed by the General Assembly of the United Nations on 10 December 1948", which is the provides for a notion of "human dignity".

[202] Preamble Oviedo Convention: The member States of the Council of Europe, the other States and the European Community, signatories hereto,… … Conscious that the misuse of biology and medicine may lead to acts endangering human dignity;… and … Resolving to take such measures as are necessary to safeguard human dignity and the fundamental rights and freedoms of the individual with regard to the application of biology and medicine,…

[203] Article 5 Oviedo Convention (Consent – General rule): "An intervention in the health field may only be carried out after the person concerned has given free and informed consent to it. This person shall beforehand be given appropriate information as to the purpose and nature of the intervention as well as on its consequences and risks. The person concerned may freely withdraw consent at any time."

[204] Ten Have and Gordijn (n 26).

[205] Andorno, 'The Oviedo Convention: A European Legal Framework at the Intersection of Human Rights and Health Law' (n 186).

[206] Article 13 Oviedo Convention (Interventions on the human genome): "An intervention seeking to modify the human genome may only be undertaken for preventive, diagnostic or therapeutic purposes and only if its aim is not to introduce any modification in the genome of any descendants."

[207] Article 14 Oviedo Convention (Non-selection of sex): "The use of techniques of medically assisted procreation shall not be allowed for the purpose of choosing a future child's sex, except where serious hereditary sex-related disease is to be avoided."

[208] Andorno, 'The Oviedo Convention: A European Legal Framework at the Intersection of Human Rights and Health Law' (n 186); Lwoff (n 189).

A precise rationale that underlies the *Oviedo Convention* is the prohibition of sex selection. Article 14 of the *Oviedo Convention*[209] prohibits that, when applying *in vitro fertilization*, the sex of the eventual child is selected unless serious hereditary diseases, which are sex-related, can be avoided. In that regard, it is important to note that, as already mentioned in Chapter 2 of this thesis, CRISPR-Cas9 can be used as a tool used for *in vitro fertilization*. Therefore, this prohibition is relevant, as well. One rationale that is behind this prohibition is that the ability to choose a child's sex, for other reasons than medical reasons, could be seen as an incentive to commodify children.[210] In other words, an absence of such a prohibition would open the door to making so-called "designer babies", which already has been described in earlier in this thesis.

Another rationale behind this prohibition is that the ability to choose a child's sex could cause an offset in the sex ration of certain populations. This could especially be the case in countries where males are favoured, due to cultural, traditional and/or economic considerations.[211] This rationale seems not to be explicitly underlying the UDBHR and UDHGHR. However, if one considers the notion of human dignity that the UDBHR and UDHGHR consider, one might conclude that this rationale implicitly underlies either piece of legislation. It could be considered that sex selection is contrary to human dignity, which is heavily protected in each piece of legislation. Hence, this rationale can also be considered found as a rationale underlying the UDBHR and UDHGHR.

[209] Article 14 Oviedo Convention (Non-selection of sex): "The use of techniques of medically assisted procreation shall not be allowed for the purpose of choosing a future child's sex, except where serious hereditary sex-related disease is to be avoided."
[210] Andorno, 'The Oviedo Convention: A European Legal Framework at the Intersection of Human Rights and Health Law' (n 186).
[211] ibid.

4. CRISPR-Cas9 and existing legal frameworks

This chapter will align the issues deriving from clinical applications of CRISPR-Cas9 on humans (as provided in Chapter Two) with the rationales that are underlying in the existing legal frameworks of the UN, EU and CoE. In cases where the issues deriving from clinical applications of CRISPR-Cas9 on humans are not addressed by these rationales, this chapter will introduce additional rationales that could be taken into account when regulating clinical applications of CRISPR-Cas9 on humans. This paragraph will start by describing the issues that are addressed by the existing legislation (e.g. rationales that underlie the existing legal frameworks regard human genome engineering). After that, this paragraph will continue by describing the issues that are not addressed by the existing legislation by stating them as additional rationales.

4.1 Issues addressed by rationales of the existing legal frameworks

One of the issues that is covered in the existing legal framework are the present safety and reliability issues. This issue can be connected to the rationale that emphasizes to increase benefit and reduce harm, as (implicitly) mentioned in the UDBHR, UDHGHR, and the *Oviedo Convention*. Since this principle requires a balancing exercise to be made it should be pointed out that, at this moment in time (May 2019), there are still significant safety and reliability issues. For instance, momentarily, there are still off-target mutations occurring.[212] On top of that, the long-term effects of these genome modifications are still to be determined.[213] There is still significant uncertainty on what these mutations might end up causing to the human genome. Currently, the effects are only known for mice, but not for humans.[214] Therefore, at this moment in time, the safety and reliability issues shall be taken into account when performing the balancing exercise.

One of the key concerns deriving from clinical applications of CRISPR-Cas9 on humans is the concept of "intergenerational equity". The concept of intergenerational equity, either as an ethical concept and as a legal rationale, strives for fairness and justice between generations. It assumes that, when something affects future generations, it does not "belong" to any generation, but it "belongs" to all generations, and requires behaviour accordingly.[215] Hence, "intergenerational equity" as an ethical issue deriving from the clinical applications of CRISPR-Cas9 on humans falls within the notion of "intergenerational equity" as a rationale, underlying the UDBHR and the *Oviedo Convention*.

[212] Bosley and others (n 5).

[213] Heidi C Howard and others, 'One Small Edit for Humans, One Giant Edit for Humankind? Points and Questions to Consider for a Responsible Way Forward for Gene Editing in Humans' (2018) 26 European Journal of Human Genetics 1.

[214] Dong Hyun Jo and others, 'Long-Term Effects of In Vivo Genome Editing in the Mouse Retina Using Campylobacter Jejuni Cas9 Expressed via Adeno-Associated Virus.' (2019) 27 Molecular therapy : the journal of the American Society of Gene Therapy 130.

[215] Edith (n 55).

Another issue identified in connection with clinical applications of CRISPR-Cas9 on humans is the notion of "human autonomy". The notion of "human autonomy" manifests itself into the concepts of "intergenerational equity" and "human dignity". On the one hand, with regard to the concept of "intergenerational equity", human autonomy is part of this concept because it is justified and substantiated by the ethical theory of *Kantianism*. According to *Kantianism*, human autonomy is the most important of the pillar of human existence and should always be taken into account.[216] This is relevant because germ line modifications constitute the possibility to alter a genetic makeup of cell that will be passed on its descendants, without the future generations being able to consent, or not. Therefore, autonomy might be taken away from said future generations. On the other hand, with regard to the concept of human dignity, autonomy serves as a pillar.[217] Again, as mentioned above, *Kantianism* for a large part shapes the current notion of human dignity. According to *Kantianism*, human autonomy is essential to ensuring that human dignity is respected.[218] Human dignity requires that humans ought not to be instrumentalised in cases where it will not benefit themselves.[219] Hence, it requires that human integrity and identity ought to be protected from misuse of (bio)technological development (i.e. misuse of the CRISPR-Cas9 technology). Thus, the characteristic of human autonomy can be connected to the rationale that emphasizes the respect for human dignity (and human rights) in the UDBHR, HDHGHR and the *Oviedo Convention*, as well as, to a certain extent, the rationale that emphasizes to respect for the principle of "intergenerational equity", as mentioned in the UDBHR and the *Oviedo Convention*.

The risk of the creation of "superhumans" was also identified in connection with clinical applications of CRISPR-Cas9 on humans. The issue of "superhumans" stresses that intentional germ line application of CRISPR-Cas9 for enhancement purposes might create "superhumans". The rationale that emphasizes to promote "justice and equality" could provide relief for this issue. The rationale that promotes "justice and equality" is, for a large part, based on the concept of distributive justice. It describes how society ought to allocate resources to a human individual that have conflicting interests, without considering the merits of the individual.[220] In essence, this rationale strives to prohibit and prevent the selective accessibility to the technology. Hence, the rationale of "justice and equality" as mentioned in the UDBHR can be related to the risks of creating "superhumans" and, furthermore, to the risks of enhanced warfare, as well as the creation of different classes of enhanced humans, based on wealth and access to CRISPR-Cas9. In essence, this rationale aims to establish that certain resources (e.g. CRISPR-Cas9 clinical applications) are distributed among humans in a just and equal manner.[221] This means that clinical applications of CRISPR-Cas9 ought to be distributed in a manner which is fair to all. Consequently, this rationale requires that those most in need, receive the CRISPR-treatment, regardless of wealth.

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[216] Andorno, 'Human Dignity and Human Rights' (n 107).
[217] ibid.
[218] Kant (n 113).
[219] Andorno, 'Human Dignity and Human Rights' (n 107); Kant (n 113).
[220] Neves (n 142); Aristotle (n 143); Rawls (n 148).
[221] Neves (n 142); Aristotle (n 143); Rawls (n 148).

Nonetheless, not only the rationale that emphasizes to promote "justice and equality" could provide relief for the issue of "different classes of humans". Alternatively, the rationale that prohibits "sex selection" could provide relief for the issue of "different classes of humans". This rationale prohibits the selection of the sex of a child unless serious hereditary diseases, which are sex-related, can be avoided.[222] Mainly, this principle aims to preserve human diversity.

About the risk of unfair warfare, the rationale that emphasizes to respect "human dignity (and human rights)" could provide relief for this issue. As mentioned above, the current notion of human dignity is for a large part shaped by *Kantianism*.[223] According to *Kantianism*, humans always have to be treated as an end and never merely as a means to an end. Essentially, humans ought not to be instrumentalised in cases where it will not benefit themselves.[224] However, in the case of the issue of "unfair warfare", humans are instrumentalized – for war purposes – without themselves (directly) benefiting from it. Therefore, "unfair warfare" could be considered contrary to human dignity.

For the sake of completeness, a scheme is provided hereafter, in order to get an overview of how the issues are addressed by the rationales that underlie the existing legal frameworks (see Figure 6).

Issues		**Rationales**
Safety and Reliability	→	Benefit and Harm
Intergenerational Equity	→	Intergenerational Equity
Autonomy	→	Human Dignity and Intergenerational Equity
Superhumans	→	Justice and Equality
Different Classes of Humans	→	Justice and Equality and Sex Selection
Unfair Warfare	→	Human Dignity

Figure 6 – Overview of issues addressed by rationales

4.2 Issues not addressed by rationales existing legal frameworks

When analysing issues raised by the clinical applications of CRISPR-Cas9 on humans in the light of the existing legal frameworks, it can be concluded that the existing legal framework serves as well a legal basis. Thus, it is sufficient to mitigate certain ethical and societal frictions that there emerge from the clinical applications of CRISPR-Cas9 on humans, as described above. However, the existing legal frameworks are not sufficient to cover some other issues deriving from clinical applications of CRISPR-Cas9 on humans.

One of those shortcomings concerns the ability of the existing legal frameworks to cope with the issues deriving from the accessibility (e.g. inexpensiveness) of the CRISPR-Cas9

[222] Andorno, 'The Oviedo Convention: A European Legal Framework at the Intersection of Human Rights and Health Law' (n 186).
[223] Andorno, 'Human Dignity and Human Rights' (n 107).
[224] Kant (n 113).

technology. Badly-modified cells could (ultimately and potentially) be harmful to the health of the human species. It is reasonably plausible that the legal frameworks are not able to cope with these frictions because the UNESCO Universal Declaration on Bioethics and Human Rights and UNESCO Universal Declaration on the Human Genome and Human Rights, and *Oviedo Convention*, as already mentioned in Chapter Three, merely set out principles and standards and are based on technologies that require significant investments and expertise. These issues are likely to be solved by more specific legislation, using said conventions as baseline and guidelines.

One more issue that the existing legal framework is not able to cope with is the concept of "forum shopping" or "genome tourism". In order to prevent "forum shopping" or "genome tourism" practices, it is necessary for legislators, policymakers and politicians at globally level to reach consensus on regulating clinical applications of CRISPR-Cas9 on humans in order to avoid creating a from scattered and incongruent legal framework worldwide.

Another issue that needs to be taken into consideration when making regulatory choices is the so-called *Collingridge dilemma*. This dilemma implies that there is a trade-off between the convenience of influencing and/or controlling the development of a technology and knowing the impact of that technology.[225] Public acceptance of technology is a crucial feature in this matter. In order not to hinder the development of CRISPR-Cas9 technology, it is of utmost importance that the public is appropriately informed in order for it to accept or reject the technology. Research in the United States suggests that, when properly informed, the public is favourable towards human genome modification when it is for therapy purposes, but would not tolerate modifications for enhancement purposes.[226] Accordingly, it would be less likely that the development of the technology would be hindered. On top of that, when the medical potential of CRISPR-Cas9 is considered, it seems only appropriate that a careful choice in this regard is to be made. Scientists fear that an exaggerated public view on CRISPR-Cas9 would cause a backlash to the technology, as society might think that CRISPR-Cas9 would lead to science fiction scenarios and could have a bunch of unanticipated and undesirable effects. These views might create fear, distrust and overcaution on the use of CRISPR-Cas9.[227] Consequently, this might cause that the scientific community is no longer able or no longer willing to conduct research into the CRISPR-Cas9 technology. This could put a stop to the development of CRISPR-Cas9 the technology, and frustrating for the (medical) potential to be achieved. For these reasons, informing the general public is of fundamental importance.

Should legislators choose to not regulate, due to the lack of oversight and the accessibility of the CRISPR-Cas9 technology, the door could be open to "rogue scientists", as shown by the case of He Jiankui.[228] Consequently, the safety of humans could be in danger, as there would

[225] Collingridge (n 83).

[226] This research indicates that two thirds of Americans support human gene editing to cure diseases; The Associated Press - NORC Center for Public Affairs Research, 'Human Genetic Engineering' (*The Associated Press*, 2018) <http://apnorc.org/projects/Pages/Human-Genetic-Engineering.aspx> accessed 20 December 2018.

[227] Bosley and others (n 5).

[228] Regalado, 'EXCLUSIVE : Chinese Scientists Are Creating CRISPR Babies' (n 13); Robitzski (n 15).

be no safety (or quality) check on the modified cells. The non-regulation of CRISPR-Cas9 is not a viable solution. This is to say because, when the choice is made for not regulating, the technology will nonetheless still develop, whether in an undesirable manner or not. CRISPR-Cas9 has already a significant impact on the scientific realm and is widely adopted. It is likely to be the case that the CRISPR-Cas9 technology will have an even more significant impact in the future.

A final issue that needs to be taken into account is that the dichotomy between "therapy" and "enhancement" might be an irrelevant dichotomy in the future. When approaching the regulation of clinical applications of CRISPR-Cas9 on humans from an "STS" perspective[229], the assumption is that technology and society mutually shape one another. Technologies do not exist in a sort of vacuum, but that people and technology are entangled with one another, and that human and non-human actors have agency. In essence, this assumes that users can "shape" technologies according to their own preferences, which is called "technological agency".[230] It is the claim of the author that this "technological agency" would cause the dichotomy between "therapy" and "enhancement", upon which notions the current legislation, as well as ethical debates, are based, is a dichotomy and will ultimately become obsolete. What we now consider as "enhancement", is likely not be considered as such in the future. Human behaviour is essential in this regard. If humans start to use CRISPR-Cas9 as a "new aesthetic surgery", there will be no such distinction between "therapy" and "enhancement". In other words, the normalization certain uses are crucial in this regard. It would open the door to "enhancement" purposed application and would, ultimately, shift the paradigms of the purposes, making the distinction between "therapy" and "enhancement" obsolete.

In our contemporary societies, as research shows us, there is a normalization in the use of aesthetic surgery. For instance, the American Society of Plastic Surgeons reports a rise in body shaping and non-invasive procedures, more specifically they indicate that low-threshold cosmetic alteration surgeries, such as Botox, increased with 200 percent since 2000.[231] Moreover, research by the Boston University introduced the notion of so-called *snapchat dysmorphia*.[232] The notion identifies that people have the need to look like the "edited" (or "photoshopped) version of oneself. Essentially, according to scientists, it is a trend that blurs the distinction between reality and fantasy, as 55 percent of the examined patients undergo plastic surgeries in order to make better selfies.[233] Both researches indicate that there is an

[229] Ej Hackett and others, *The Handbook of Science and Technology Studies*, vol 54 (MIT Press 2008); "STS" is an abbreviation for "Science and Technology Studies". In STS, the supposition is that science, technology and society mutually shape one another. Technology is not a neutral, but all aspects interact and influence one another.
[230] ibid.
[231] American Society of Plastic Surgeons, 'New Statistics Reveal the Shape of Plastic Surgery' (*American Society of Plastic Surgeons*, 2018) <https://www.plasticsurgery.org/news/press-releases/new-statistics-reveal-the-shape-of-plastic-surgery> accessed 29 March 2019.
[232] Susruthi Rajanala, Mayra BC Maymone and Neelam A Vashi, 'Selfies — Living in the Era of Filtered Photographs' (2018) 20 JAMA Facial Plastic Surgery 443.
[233] ibid.

increasing normalization in aesthetic surgeries and indicates that people consider their outer appearance as increasingly important.

Evidently, this regards surgeries and not human genome modification so that it might seem far-fetched at first sight. However, it could be that the phenomenon of people setting new standards could happen to human genome engineering as well, as already is described by the issue of the "slippery slope". It could be the case that people could take up a different definition of what is to be considered normal and what is not. Since people will set new standards that match their "realities", every enhancement can be considered acceptable, or even therapeutic, which makes the "slippery slope" issue reality. The "slippery slope" issue stresses that applications of genome engineering might shift from "therapy purposes" towards "enhancement purposes". However, what is actually the definition of "therapy", or "enhancement"? The literature seems to suggest that, as mentioned earlier, "therapy" is (more or less) the same as "disease-curing" or "correcting" and that all the rest is "enhancement". However, what is actually a "disease" or "correcting"? Are sunglasses or welding helmets to be considered as "enhancement" or "therapy"? Probably it would currently be considered as "therapy", which is likely because sunglasses and welding helmets are socially accepted and have been used for decennia. But what happens if one changes the genome in such a way that it results in the eye being resistant to ultraviolet light, which would make the sunglasses or welding helmet of no use? Would it still be considered "therapy"? Essentially, no average, healthy person would able to have eyes which are naturally ultraviolet light resistant. This might imply that it cannot be qualified as "therapy" and will be qualified as "enhancement". This is just a simple example, but this could be the starting point for the "slippery slope" to occur, which would make the distinction between "therapy" and "enhancement" obsolete.

The view of Harari supports the claim of the author. As Harari describes in his book *Homo Deus*[234], history tells us that people will reinterpret definitions in order to justify their behaviour. Harari describes that, starting from the Agricultural Revolution people justified the behaviour by stating that they behaved "in the name of God". For most people, this was plausible as they believed that God was their explanation of why humans were "special", and God was the one to mediate between nature and humans.[235] Harari claims that these fictions are present in order to make the system work. However, he claims that those fictions do not represent reality. He argues that fictions should be tools rather than goals or yardsticks.[236] Harari reiterates that it is essential to realize that they remain fictions; otherwise, humans would lose touch with reality. Harari argues that fictions are invented to serve us, rather than the other way around. He claims that the distinction between fiction and reality will blur and people reshape reality to match their fictions.[237] The author claims that, by the use of the technology, the same phenomenon as described by Harari will occur over time regarding human genome modification, because people will redefine these fictions in order to match their new "reality".

[234] Yuval N Harari, *Homo Deus: A Brief History of Tomorrow.* (Vintage 2016).
[235] ibid.
[236] ibid.
[237] ibid.

Hence, the definitions of "therapy" and "enhancement" are (ultimately) mere fictions in order to make the system work, but do not represent future reality. Therefore, this is an issue which could be taken into account when regulating clinical applications of CRISPR-Cas9 on humans.

5. Conclusions

In this chapter, the main research question of this research will be answered. This will be done so by, first, demonstrating the concept of the research. Thereafter, the outcome of the research will be provided. And, finally, the implications of the research will be provided.

5.1 Concept of the research

Already in 2015, scientists in the realm of human genome engineering published a consensus statement, stating that genome engineering is irresponsible until a broad societal consensus is achieved on the appropriateness of the applications of GETs for clinical applications on humans. Recently, this 2015 consensus statement gained momentum and seems to become alive again. This is to say because, in response to the He Jiankui experiment, an incredible number of scientists from all around the world expressed their concerns. They call, like the United Nations, for a moratorium on germ line modifications of human genomes, as well as call for global rules on human genome modifications.

Regarding the aforementioned, several quantitative researches have shown that there is little to no harmonization of rules on human genome engineering, as countries (to a large extent) set out different rules. The researches indicate that there are various types of legal interventions (e.g. the number of pieces of legislation) and types regulations (e.g. guidelines or more binding rules), either at the state-level or super-state level. Subsequently, the research claims that the existing EU and CoE legal frameworks governing human genome engineering, are not *sufficient* nor *effective* to regulate clinical applications CRISPR-Cas9 on humans, which is due to the very nature of the CRISPR-Cas9 technology. Thus, it seems to be that the case that these researches confirm and underline the consensus that renowned scientists achieved in 2015, as well as recently. In other words, the gap in the literature is, in essence, that existing legislation would not be *sufficient* nor *effective* to regulate clinical applications of CRISPR-Cas9 on humans. Hence, it is desirable to find common ground through (globally) accepted rationales in order to regulate clinical applications of CRISPR-Cas9 on humans.

In order to address the existing problem as mentioned above, this thesis aimed to provide legislators in the EU with a conceptual basis in order to regulate clinical application of CRISPR-Cas9 on humans. This thesis has done so by providing rationales, through the following main research question: "*Which rationales could the EU take into account when regulating clinical applications of genome engineering technology CRISPR-Cas9 on humans?*". The aforementioned main research question common thread of this research, and, thus, will be answered hereafter.

5.2 Outcome of the research

This research concludes there are various rationales that the European Union could take into account when regulating clinical applications of genome engineering technology CRISPR-Cas9 on humans. These rationales are the following.

Human dignity

The main rationale that should be taken into account is that of "human dignity". This rationale requires that each human being holds a certain intrinsic value that ought to be respected. With regard to clinical applications of CRISPR-Cas9 on humans, two key sub-features of the notion of human dignity are particularly relevant, namely: "human autonomy" and "non-instrumentalization of humans". The notion of "human autonomy" entails that humans should remain autonomous in deciding whether or not they want their genomes to be edited. The notion of "non-instrumentalization of humans" requires that humans are not to be merely treated as a means to end.[238] Thus, it requires that human integrity, intrinsic value, and identity ought to be protected from misuse of the CRISPR-Cas9 technology.

Intergenerational Equity

Subsequently, another rationale, which is related to the aforementioned dignity, that should be taken into account, is the rationale of the "intergenerational equity". The notion of "intergenerational equity" strives for fairness and justice between generations. In particular, it assumes that, when something affects future generations, it does not "belong" to any generation, but, instead, it "belongs" to all generations, and requires to behave accordingly.

Increasing Benefit and Reducing Harm

Furthermore, another rationale that should be taken into account is the rationale of "increasing benefit and reducing harm". The concept of "increasing benefit and reducing harm" entails that a (medical) treatment should strive for the highest benefit and the least harm to be caused. This rationale requires a balancing exercise to be performed. When performing this balancing exercise, particular attention should be given to the fact, at this moment in time (May 2019), there are still (grave) safety and reliability issues (i.e. off-target mutations) with regard to clinical applications of CRISPR-Cas9 on humans.

Justice and equality

Additionally, another rationale that should be taken into account is the rationale of promoting "justice and equality". This rationale attempts to assure that certain resources (e.g. CRISPR-Cas9 clinical applications) are distributed among humans in a just and equal manner. Mainly, this rationale aims to prohibit and prevent the existence of different classes of people due to selective accessibility to the technology.

Sex selection

Another rationale, which relates to the one above mentioned, that should be taken into account is the rationale of prohibiting sex selection. This prohibition entails a ban to the selection of the sex of a child unless serious hereditary diseases, which are sex-related, can be avoided. It aims at prohibiting the ability to choose a child's sex, for other reasons than medical reasons,

[238] Andorno, 'Human Dignity and Human Rights' (n 107); Kant (n 113).

in an act of discrimination and commodification of children which might cause an offset in the sex ration of certain populations.[239] In essence, this principle aims to preserve human diversity.

Next to the rationales that underlie the existing legal frameworks, there are still some issues that the existing legal frameworks do not address. It concerns the following issues.

Accessibility of CRISPR-Cas9
Another issue to be taken into account is related to the accessibility of the CRISPR-Cas9 technology as such. Due to the technical characteristics (e.g. inexpensiveness) of the CRISPR-Cas9 technology, the technology is relatively accessible for anyone to use it. This circumstance entails the possibility for the lack of safety (or quality) of the modifications.

"Forum shopping" or "genome tourism"
One more issue, which is closely aligned with the aforementioned that is to be taken into account is so-called "forum shopping" or "genome tourism". This concept entails that if the legislation in country X allows certain behaviours, whereas the legislation of country Y prohibits certain behaviours, people will choose country X because that jurisdiction is less restrictive. In order to prevent this phenomenon from occurring, it is necessary for legislators, policymakers and politicians (globally) to reach consensus.

Collingridge dilemma and technological development
Additionally, another issue is to be taken into account concerns the *Collingridge dilemma*. On the one hand, in order to avoid another Thalidomide (or Contergan) crisis or prevent Josef Mengele-like practices, as well as to cope with the ethical and social frictions around the clinical applications of CRISPR-Cas9 on humans, a regulatory intervention might be appropriate. On the other hand, however, if CRISPR-Cas9 is regulated at an early stage, it could be possible that the technological development is hindered. This could put a stop to the development of CRISPR-Cas9 technology, and frustrating the medical potential to be achieved.

Dichotomy of "therapy" and "enhancement"
Finally, the last issue is to be taken into account is regards the existing dichotomy between "therapy" and "enhancement", as the distinction between both concepts will ultimately become obsolete. This issue assumes that the CRISPR-Cas9 technology has a certain "agency". In essence, this means that users can be instrumental in how technology is perceived by society. This "technological agency" would cause that distinction between "therapy" and "enhancement", upon which notions the current legislation, as well in ethical debates are based, will become obsolete. This is to say because over the past years, as research has shown, the world underwent a normalization of aesthetic surgeries. This is likely to be the case as well with regard to "therapy" and "enhancement". Because what we now consider as either "therapy" or "enhancement", is likely not be considered as such in the future due to the normalization of the use of the technology for certain purposes. Essentially, with this

[239] Andorno, 'The Oviedo Convention: A European Legal Framework at the Intersection of Human Rights and Health Law' (n 186).

assumption comes the realization of the so-called "slippery slope" concerns, as every enhancement can be considered acceptable, or even therapeutic. Consequently, as Harari also mentioned, humans will lose touch with reality if they stick to the distinction between "therapy" and "enhancement", as the difference between fiction and reality will blur, and people will reshape reality to match their fictions. Hence, this is an issue which could be taken into account when regulating clinical applications of CRISPR-Cas9 on humans.

In this paragraph, the rationales that the European Union could take into account when regulating clinical applications of genome engineering technology CRISPR-Cas9 on humans were identified. Hereunder, in Figure 7, an overview is provided on which rationales the European Union could take into account when regulating clinical applications of genome engineering technology CRISPR-Cas9 on humans.

RATIONALES	ISSUES
Human Dignity	Accessibility of CRISPR-Cas9
Intergenerational Equity	Forum Shopping or Genome Tourism
Increasing Benefit and Reducing Harm	Collingridge Dilemma and Technological Development
Justice and Equality	
Sex Selection	Dichotomy of "Therapy" and "Enhancement"

Figure 7 – Overview of rationales

5.3 Implications of the research

As mentioned above, this research provides legislators in the EU with a conceptual basis in order to regulate clinical application of CRISPR-Cas9 on humans, using rationales and highlighting the important issues. In that regard, it is important to highlight that this research merely provides a conceptual (underlying) basis. This research merely assessed standard-setting and principle-setting treaties (e.g. UDBHR, UDHGHR and the *Oviedo Convention*), from which it can be extremely to derive hard, concrete (legal) obligations. Consequently, further research ought to be conducted into how this underlying, conceptual basis, can be best incorporated into more specific and binding legal rules.

In line with the aforementioned it is important to point out that the current conceptual basis, as researched for herein, is for a large part based on non-binding rules. When one examines this conceptual basis, one could see that a large part of it finds its origin in the UDBHR, which is non-binding. It is up to future research to research whether or not it is effective and/or necessary to translate this conceptual basis into (more) binding provisions.

Moreover, in order to mitigate the practical issues deriving from the accessibility of the CRISPR-Cas9 technology as such, further research ought to be conducted. The current legal frameworks are not capable of addressing the undesired effects deriving from the accessibility of the CRISPR-Cas9 technology. In order to mitigate this concern, further research needs to be conducted into what the most effective way is to mitigate these concerns.

In conclusion, this research is only the first step into regulating clinical applications of CRISPR-Cas9 on humans *sufficient*ly and *effective*ly. By setting out an underlying conceptual basis for legislation, only a "stepping stone" is provided. It is up to future researches to provide for the next step(s).

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List of Abbreviations

Abbreviation	Meaning
CoE	Council of Europe
CRISPR	Literally: "*Clustered Regularly Interspaced Short Palindromic Repeats*", but also: the CRISPR-Cas9 technology as such
EU	European Union
GETs	Genome engineering technologies
GMOs	Genetic Modified Organisms
IBC	International Bioethics Committee
IVF	*In vitro fertilizations*
MIT	Massachusetts Institute of Technology
MS	Member States
Oviedo Convention	Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine
QALYs	Quality adjusted life years
TALENs	Transcription activator-like effector nucleases
UDBHR	UNESCO Universal Declaration on Bioethics and Human Rights
UDHGHR	UNESCO Universal Declaration on the Human Genome and Human Rights
UDHR	UNESCO Universal Declaration on Human Rights
UN	United Nations
UNESCO	United Nations Education, Scientific and Cultural Organization
ZFNs	Zincfinger nucleases