



Genome editing in humans

A survey of law,
regulation and
governance
principles

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Genome editing in humans

A survey of law, regulation and governance principles

Genome editing is a powerful new tool for making precise additions, deletions and substitutions in the genome. The development of new approaches has made editing of the genome much more precise, efficient, flexible and less expensive, relative to previous strategies.

As with other medical advances, each such application comes with its own set of benefits, risks, ethical issues and societal implications, which may require new regulatory frameworks. Important questions raised with respect to genome editing include how to balance potential benefits against the risk of unintended harms; how to govern the use of these technologies; and how to incorporate societal values into salient clinical and policy considerations.

This STOA study provides an overview of human genome-editing applications and a review of the principles that guide the governance of genome editing in humans, at EU level and worldwide. The study also formulates a series of policy options targeted at basic research and clinical applications, both somatic and germline.

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Executive summary

Genome editing is a powerful new tool allowing precise alterations in the genome. The development of new approaches based on the CRISPR-Cas9 system has made this process much more efficient, flexible and affordable, relative to previous strategies.

These technological advances originated in remarkable interest in possible applications, both in fundamental research and in the treatment or prevention of disease and disability. Possibilities range from restoring normal function in diseased organs by editing somatic cells to preventing genetic diseases in future children and their descendants by editing the human germline.

As with other medical breakthroughs, each such application comes with its own set of risks, benefits, ethical issues and societal implications, which may require the revision of existing regulatory frameworks. Important questions raised include how to balance potential benefits against unintended harms, how to govern the use of these technologies, how to incorporate societal values into relevant clinical and policy applications, and how to respect the inevitable cultural specificities that shape the future direction of the use of these technologies.

The goal of this study was therefore to provide an overview of the state-of-the-art of the science, as well as an analysis of current and projected regulatory, ethical, legal and social implications. Based on these findings, policy options were provided.

The internal market for health and 'wellness' services and products can and is already subject to considerable harmonisation in the European Union. Provided that there is sufficient consensus, there is ample room to either introduce genome editing-related provisions in existing directives and regulations (vertical approach), or to enact specific genome-editing legislation (horizontal approach). Besides legislative intervention, it is also possible to explore alternative or cumulative public and private governance mechanisms.

Harmonised definitions would be beneficial to the internal market for health and wellness services and products. These facilitate legal certainty in the internal market, improving the prospects for citizens (as patients and consumers), companies and healthcare providers (public or private) to navigate the different national rules and a fragmented legal landscape. Uniform definitions facilitate comparison and organic approximation of national legislation, policies, and governance structures.

Legal definitions should include appropriate resilience mechanisms to ensure sustained correspondence with scientific knowledge. From a regulatory perspective, the use of qualifiers such as '**somatic versus germline**', '**hereditary**' genome editing, or '**modifying genetic identity**', is considered scientifically outdated, vague and prone to differing legal interpretations. Somatic as well as germline applications may carry associated dangers. Once clinical safety is established, germline interventions could also have strong therapeutic potential. Possible horizontal harmonisation approaches could include, for example, maintaining a general prohibition, in which the clinical risk-benefit ratio is unacceptable and, additionally, clarifying concepts and, most importantly, creating exceptions for research and future treatments of serious diseases.

Regarding genetic eugenics prohibited by Article 3 of the EU Charter of Fundamental Rights, this study proposes the option of regulation to expressly clarify or extend the prohibition to the actions of private actors and to somatic interventions where these cannot be considered to be the result of informed and free consent, and simultaneously clearly exempting preventive and precision medicine.

Regarding advanced therapeutic product regulation, genome-editing products are currently subject to a centralised approval procedure, but exceptions are decided locally. One option would be to further harmonise exceptions granting patients early access, e.g. compassionate use, named-patient use and hospital exceptions.

As for genome editing in assisted reproduction techniques, rules and proposals to allow editing are often linked with the treatment of serious diseases. There is an urgent need to define and, if possible, harmonise science-based criteria used to determine the seriousness of a given disease, including both from a patient-centric perspective and using medical diagnosis elements.

Uncontrolled somatic editing can pose great social and ethical risks (e.g., inequality, public health problems, interventions in children and people unable to consent, discrimination, etc.). Regarding wellness and cosmetic somatic editing (including enhancement), strict regulatory framework for market approval only applies to products used for the treatment, prevention or diagnosis of a disease. The use of 'human enhancement' as a criterion for unacceptable interventions is not useful, as it is too vague, value-charged and difficult to enforce. An option would be to ensure public health prevention by determining types of editing that should be prohibited or restricted, practitioners' professional qualifications, safety and technical requirements. Also here, a multi-level, risk-based approach would allow specific rules to be defined for prohibited and high-risk genome-editing interventions. Possible criteria could include the objectives of the intervention, expected outcomes and levels of risk for individuals and society.

Regarding medical/reproductive travel and beauty/wellness tourism, some countries have more permissive legislation or lack the ability to enforce rules. Restrictions should not hamper access to experimental or recently approved therapeutic options, including the participation in clinical trials. Possible options include the extraterritorial application of EU and Member State law to procedures performed abroad (provided that fundamental rights and freedoms are respected).

As for enforcement and forensic activities, the enforcement of prohibitions needs to account for fundamental rights and freedoms. An option would be to balance the needs for prevention and reintegration relating to the specific illicit conduct with the legal rights, interest and well-being of the victim. Secondly, subjects of illicit genome editing could be treated as victims and could be specifically allowed to refuse privacy or forensic activities invasive to their physical integrity. The long-term monitoring and inclusion in registries must also respect the rights to privacy, family life, personal integrity and autonomy.

Counterfeited or falsified services and products are a known intellectual property rights (IPR) and a public health issue. Genome editing could be included in the sphere of measures included when tackling this problem. Private governance through technology-licensing agreements already plays an important governance role. This study identifies an option to develop general guidance or model clauses for ethical licensing. The use of artificial intelligence (AI) systems for genome editing is a future area of concern and should be the object of consideration in AI-related regulation.

In conclusion, this study shows that while genome editing is the source of great expectations for the medical field, several ethical, social and legal questions remain to be addressed. Regulatory and governance mechanisms are greatly needed in the EU.

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List of abbreviations

Acr	anti-CRISPR
AI	artificial intelligence
AMR	Antimicrobial resistance
Cas	CRISPR-associated protein
CFTR	transmembrane regulator gene
CJEU	Court of Justice of the European Union
CoE	Council of Europe
CRISPR	Clustered Regularly Interspaced Short Palindromic Repeats
DMD	Duchenne muscular dystrophy
DNA	deoxyribonucleic acid
EGE	European Group on Ethics
ESchG	Embryo Protection Act
hESCs	human embryonic stem cells
IPR	intellectual-property rights
iPSCs	induced pluripotent stem cells
KDKs	cyclin-dependent kinases
MRSA	methicillin-resistant <i>Staphylococcus aureus</i>
RNA	ribonucleic acid
gRNA	single guide RNA
TALENs	transcription activator-like effector nucleases
WHO	World Health Organisation
ZFNs	zinc-finger nucleases

Part I: Overview of genome editing applications

1. Introduction: Genome-editing applications

1.1. Genome-editing techniques

1.1.1. The CRISPR-Cas system

Genome editing is a powerful technology that allows making precise additions, deletions and substitutions in the genome, as well as regulating the activation or inactivation of gene expression.

Several genome-editing tools exist, such as meganucleases, zinc-finger nucleases (ZFNs), transcription activator-like effector nucleases (TALENs) and Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) systems. The most successful of these is the CRISPR-Cas9 (CRISPR-associated protein 9) system.

The CRISPR-Cas9 system has revolutionised the field of genome editing ever since its discovery in 2012. These 'genetic scissors' are easier to engineer, more efficient in methodology and more precise in the genome sequence being targeted. Its advantages over previous genetic engineering systems became so evident in such a short amount of time that, less than 10 years after its discovery, researchers Emmanuelle Charpentier and Jennifer A. Doudna had received the 2020 Nobel Prize in Chemistry 'for the development of a method for genome editing' (The Nobel Prize, 2020).

1.1.2. How does CRISPR-Cas9 work?

The CRISPR-Cas9 system occurs naturally in many bacteria and archaea (Bondy-Denomy et al, 2020) as an adaptive defence system, a sort of rudimentary 'immune system' that helps fight against the direct attack of common bacterial predators, be them bacteria (via plasmids) or 'bacteriophages' (viruses that attack bacteria) (Bondy-Denomy et al, 2020). This RNA interference system had been known to researchers since 1987 (Makarova et al, 2006). The novelty was the ability to harness and exploit it artificially as a genetic engineering tool to edit virtually any genome, with applications extending from human health to plant technology.

CRISPR-Cas9 technology allows introducing precise changes in a desired genome by creating double-stranded breaks in a specific DNA sequence and then allowing the cells' own DNA repair mechanisms to work. The system itself is composed of two components: an RNA molecule called 'single guide RNA', or sgRNA, and a protein called Cas9, for "CRISPR-associated protein 9", which introduces a site-specific double-strand break in the DNA.

1-The first step in the engineering process is the artificial design of the specific RNA sequence (single guide RNA, or sgRNA) that will recognise the specific target DNA in the human cell. This step can be designed by a researcher on any normal computer using bioinformatics software.

2-Then, the CRISPR system must be delivered to human cells, which can be done via lipofection, injection or electroporation (van der Oost et al, 2016).

3-Once inside the target human cell, the guide RNA will recognise and bind to the target DNA sequence the researcher wants to modify.

4-Then, the Cas9 protein will cleave the DNA at the chosen location.

5-As a final step, the natural DNA repair mechanisms of the human cell will help replace the previous DNA with the new version.

For more information on the mode of functioning of the CRISPR-Cas9 system, please see STOA publication 'Genome edited crops and 21st century food systems challenges'.

1.1.3. Other systems

Roughly around the same time Jennifer Doudna and Emmanuelle Charpentier designed the synthetic RNA of the CRISPR-Cas9 technology, Feng Zhang optimised protein Cas9 for *in vivo* use. His team has since isolated proteins Cas12 and Cas13 (Yan, Wang & Zhang, 2019) from two bacterial strains. These show certain technical advantages over Cas9, namely, the ability to perform multiplex genome editing (Cas12), increasing specificity and thus lowering the possibility of off-target effects (Paul & Montoya, 2020), and the ability to cleave RNA instead of DNA (Cas13), thus allowing for more specific modulation of protein-production levels (King-Jones et al, 2020), although being more susceptible to off-target effects compared to Cas9.

2. Applications of genome-editing technologies

Since its discovery in 2011, CRISPR-Cas technology has immediately revolutionised research as an easy-to-use, fast and accurate technology and allows making precise changes in any genome. It is now possible to easily and accurately make a single nucleotide change in a gene, replace, delete or add entire genes, rearrange chromosomes and activate or deactivate the expression of genes.

Several fields can potentially be revolutionised by the CRISPR-Cas technology, ranging from biological research, research and development, human medicine, biotechnology and agriculture. An example is the dairy industry, where CRISPR-Cas9 is already used to immunise lactic acid bacteria against phages.

CRISPR-Cas9 can also be used as an alternative to animal testing, as it is faster and less expensive than traditional animal testing, thus providing faster development of pharmaceutical products. Cells and organisms that have been engineered using CRISPR-Cas9 include cell lines and model organisms used in biological research (mice and rats, fruit flies, nematodes, *Arabidopsis*, salamanders, frogs, monkeys); crop plants (rice, wheat, sorghum and tobacco) and fungi (*Kluyveromyces*, *Chlamydomonas*) in biotechnology, and organoids, human embryonic stem cells (hESCs) and induced pluripotent stem cells (iPSCs) in the field of biomedicine (Doudna & Charpentier, 2014).

However, policy makers have shown concern over the indiscriminate use of this technology in human health applications and potential ethical and legal issues. The risks and potentials of this technology have not been thoroughly assessed.

2.1. CRISPR-Cas in biomedicine

CRISPR editing has been at the centre of much discussion concerning how genome editing could be applied to promote human health. In biomedicine, genome editing in human cells could be used for four purposes: basic research, somatic interventions, stem cell interventions and biological enhancement.

2.1.1. Basic research

Basic research involving genome editing of human cells and tissues is critical to the advancement of biomedical science. Genome editing research using somatic cells can advance the understanding

of molecular processes that control disease development and progression, potentially facilitating the ability to develop better interventions for affected people. Laboratory research involving genome editing of germline cells can help in understanding human development and fertility, thereby supporting advances in such areas as regenerative medicine and fertility treatment.

2.1.2. Somatic interventions

Somatic cells are all those present in the tissues of the body except for sperm and egg cells and their precursors. This means that the effects of genome editing of somatic cells are limited to the treated individuals and are not inherited by their offspring. The idea of making genetic changes to somatic cells—referred to as 'gene therapy'—is not new, and genome editing for somatic applications would be similar. Besides treatment of rare Mendelian-inherited diseases (single-gene diseases) that affect one main organ or tissue, several countries (e.g. China, USA) have already started clinical trials for untreatable cancer conditions in human patients. In addition, potential treatments for difficult-to-treat infectious diseases are underway.

2.1.3. Germline interventions

Although editing of an individual's germline (reproductive cells) has been achieved in animals, there are major technical challenges to be addressed in developing this technology for safe and predictable use in humans. The most relevant technical issues relate to the uncertainty resulting from the cell-dependent DNA repair processes triggered by the double-strand break lesion caused by the CRISPR system. Up to now, there is no absolute control of the outcome. Many different alleles can be generated from a single CRISPR intervention and organisms become mosaics, since they carry cells with different sequences in the target DNA. Nonetheless, the technology is of interest because thousands of inherited diseases are caused by mutations in single genes. Thus, editing the germline cells of individuals who carry these mutations could allow them to have genetically-related children without the risk of passing on these conditions. Yet, the technique must be either devised so that the organism (the patient) can tolerate the presence of different alleles, or else, must be optimised until it is fully under control.

2.1.4. Elective interventions

Although much of the current discussion around genome editing focuses on how these technologies can be used to treat or prevent disease and disability, some aspects of the public debate concern other purposes, such as the possibility to enhance traits and capacities beyond levels considered typical of adequate health. In theory, genome editing for such enhancement purposes could involve both somatic and germline cells. Such technological uses raise questions of fairness, social norms, personal autonomy and the role of public and private governance.

2.1.5. CRISPR-Cas as therapeutic option against cancer

Diseases that could be potentially treated by CRISPR-Cas systems include cancer, allergies and immunological diseases, Duchenne muscular dystrophy (DMD), cardiovascular, neurological and metabolic disorders (Sharma et al, 2021).

Cancer is reported by the World Health Organisation (WHO) as a leading cause of death worldwide, accounting for 10 million deaths in 2020 (WHO Factsheet, 2022). Current approaches to fight cancer, such as chemotherapy, are often unspecific and relatively toxic. In this regard, CRISPR-Cas has emerged as a promising novel technology with potential to target mutated oncogenes and tumour-suppressor genes.

Current CRISPR-Cas technology applied to cancer research has shown efficacy in blocking bladder cancer cell proliferation and in inducing apoptosis. In addition, it was possible to delete an entire gene responsible for causing myeloid cell leukaemia (Liu et al, 2014). Thirdly, cyclin-dependent kinases (KDKs), which regulate our cell cycles and whose malfunctioning can often lead to cancer, could be silenced by CRISPR-Cas in the treatment of osteosarcoma and breast cancer. Challenges still to be tackled include limiting off-target effects and increasing efficacy and delivery methods (Chen et al, 2020).

2.1.6. CRISPR-Cas as potential answer to antimicrobial resistance

Antimicrobial resistance (AMR) is also a serious health threat associated to infections caused by bacteria, parasites, viruses and fungi. Drug-resistant diseases currently cause 700 000 deaths per year and the prediction is for them to reach 10 million deaths per year by 2050, especially in high-income countries (IACG, 2019).

CRISPR-Cas was shown to be able to knock-down the expression of a multidrug resistance (MDR) gene that leads to chemotherapeutic drug resistance (Liu et al, 2016). Similarly, a few studies have shown CRISPR-Cas potential as therapeutic agent against AMR pathogens, with the added advantage over current use antimicrobials of increased target specificity (Kiga et al, 2020; Duan et al, 2021). However, such application remains at a very early stage. One drawback is that resistance to CRISPR-Cas itself has been observed, with reports that it could even accelerate antimicrobial resistance in methicillin-resistant *Staphylococcus aureus* (MRSA) (Mo et al, 2021).

2.1.7. CRISPR-Cas as therapeutic option for single-cell diseases

Some major genetic conditions result from mutations in a single gene. A few examples are diseases such as cystic fibrosis, sickle cell disease and Duchenne muscular dystrophy (DMD), which affect up to 250 million individuals globally and cause considerable financial damage (Doudna, 2020). CRISPR-Cas has potential as a new therapeutic option against these conditions.

Cystic fibrosis

Cystic fibrosis is a debilitating genetic disease affecting 70 000 people worldwide. It is caused by one or several mutations in the transmembrane regulator gene CFTR, making it the most common autosomal recessive disease in Europe. A body of research has gone into studying a possible cure, so far with limited results. Gene therapy using either zinc-finger nucleases or CRISPR-Cas has allowed copying the health copy of the CFTR gene from into target human cells (Crane et al, 2015; Sharma et al, 2021). A newer study has used the primer editing technique, a newer version of CRISPR-Cas9 where Cas9 is fused to a reverse transcriptase, to correct CFTR mutations in human stem cells. This technique is arguably safer than CRISPR-Cas9 due to completely eliminating off-target effects (Maarten et al, 2021). However, results have so far been discouraging, due to the low efficacy of gene delivery into target cells and lack of studies on cell delivery altogether.

Sickle cell disease

Sickle cell disease is a type of genetic anaemic condition caused by a mutation in the beta-globin gene, leading to the formation of a haemoglobin with abnormal configuration (sickle-shaped). 90% people do not survive past 20 years of age. The only known curative therapy is bone-marrow transplantation, effective in children, but transplants are difficult to obtain.

Over the past 5 years, there have been a few successful clinical assays employing CRISPR-Cas9, making sickle cell anaemia one of the first medical targets of genome editing (Frangoul et al, 2021). In addition, *ex vivo* genome editing has shown high treatment efficiency and the possibility of permanent modification of the disease-causing gene (Park & Bao, 2021). Remaining challenges include the possibility of off-target mutations and issues with delivery methods.

Duchenne muscular dystrophy (DMD)

Duchenne muscular dystrophy is a severe type of neuromuscular disease primarily affecting boys. It is caused by a mutation in the DMD gene that leads to the absence of the dystrophin protein.

There is no cure for DMD. However, CRISPR-Cas9 therapy has been shown to revert the genetic mutation entirely and thus permanently correct the disease (Sharma et al, 2021). Current challenges regard possible off-target effects, immune response activation and delivery methods (Lim, Yoon & Yokota, 2018).

2.1.8. CRISPR-Cas in the diagnosis and treatment of Covid-19

CRISPR technologies have potential to be used as diagnostic and genome-editing tools against Covid-19 and a plethora of other human viruses for which currently there is no approved treatment, such as Ebola, Zika, and Influenza (Berber et al, 2021).

Most of this potential comes from the discovery of two new Cas proteins: Cas12 and Cas13, and several detection assays have since been developed based on either Cas12 or Cas13 use (Zhan, Li & Yin, 2021). A CRISPR-Cas13 system can detect the presence of specific viral RNA: it can detect SARS-CoV-2 presence within 1 hour, with no special instrumentation and with extremely high sensitivity (Zhang et al, 2020). A CRISPR-Cas12 system can detect the presence of SARS-CoV-2 within 30 minutes, but is less sensitive (3x-7x less) than CRISPR-Cas13.

Aside from advantages as diagnostic tool, Cas12 and Cas13 can also be used as therapeutic option. In particular, Cas13 has RNA-guided RNA endonuclease activity and thus can degrade specific Covid-19 RNA (PAC-MAN system) (Safari et al, 2021). The second advantage of this system is its adaptability to treat all coronaviruses in a single shot, by targeting conserved sequences. An injection of 6 different RNA sequences could target virtually 90% of all coronaviruses (Abbott et al, 2020). Nevertheless, this study has so far been limited to bioinformatics, therefore, the efficacy of the PAC-MAN system must still be tested *in vivo*, namely in what regards delivery systems.

3. Technical issues (strengths and weaknesses)

The first clinical trial using the CRISPR-Cas system was conducted in 2016. The three major issues currently facing this new technique are: ethical, regulatory and social questions; safety, and efficiency.

3.1. Ethical, regulatory and social questions

Because technologies such as CRISPR-Cas9 have made genome editing so efficient and precise, they have opened up possible applications that have until now been viewed as largely theoretical. The speed at which the science is developing has generated considerable enthusiasm among scientists, industry, health-related advocacy organisations, and patient populations that expect benefit from these advances. It has also raised concerns among policy-makers and other interested parties as to whether appropriate systems are in place to govern the technologies and whether societal values will be reflected in how genome editing is eventually applied in practice.

Legal, regulatory and ethical considerations are explored in more detail in part II of this study.

3.2. Safety issues

Safety issues linked with the CRISPR-Cas technology include off-target effects, unexpected on-target effects, cellular toxicity and immunogenicity (Marino et al, 2020).

Off-target effects are such as the generation of unwanted mutations via insertion and deletion (indel) events in unspecific locations in the genome, which can also increase cell toxicity.

Subsequent exploration of the technique should reduce off-target events and increase specificity. One possibility to minimise off-target events is the use of algorithmic tools during the design of the optimal sgRNA molecule (Doudna & Charpentier, 2014). Toxicity could be reduced by using anti-CRISPR (Acr) proteins. These are protein inhibitors of CRISPR-Cas systems, naturally occurring in plasmids and phages (Marino et al, 2020), which act by inhibiting either DNA binding or DNA cleavage.

3.3. Efficiency

Other challenges of the CRISPR-Cas technique involve editing efficiency, which varies according to cell type and state. Possible solutions are changes in the plasmid vector, improvement of delivery systems and cellular uptake, limitation of product degradation, improvement of fitness of edited cells and immunogenic effects of Cas9.

Immunogenic effects are an important factor for efficiency. Possible solutions are finding less immunogenic delivery methods, or designing improved, less immunogenic, versions of Cas9.

As for delivery efficiency, technical options for improvement include improvements in viral vectors or use of non-viral vectors (Cheng et al, 2020).

Part II: Principles to guide the governance of human genome editing

1. Introduction

Recent advances in genome editing offer the possibility for making precise additions, deletions and substitutions to the human genome. The technology is not new, but recent advances such as CRISPR/CasX made genome editing more efficient and precise, opening for potential applications that were until recently only theoretical.

Human genome editing, as other technological developments, imply legal questions and debate – new or re-casted – but rarely fall under a complete absence of regulation. Contemporaneous legal systems are built upon different levels of general and abstract concepts meant to be technological neutral. While existing rules may not directly nor specifically mention genome editing technologies, general principles and rules concerning interventions on the human body remain applicable. For example, through rules concerning genetic therapy, assisted reproduction techniques, medical professional rules and guidelines, regulatory procedures of approval and certification of medicinal products and patent law rules denying incentive to ethically unacceptable innovation.

Legal systems are also built upon rules, judicial practices and legal theory concerning the interpretation of legal texts and its application to specific factual circumstances. Scientific progress and further knowledge also need to be accounted for in legal interpretation. New technology creates the challenge of subsuming new technology and associated social phenomena (business models, social conducts, cultural movements) to the Law's general and abstract concepts.

The perception that Law constantly lags behind the technological development is not entirely accurate. Legal systems contain mechanisms of adaptation that ensure flexibility and resilience to change. However, in complex areas of biomedical innovation such as genome editing technology, legal concepts and their jurisprudential development risk becoming desynchronised with the state of the art of science and technology and there is need to investigate and consider enacting specific regulation or development of governance structures. Not only because new genome editing technologies afford – existing or promised – unprecedented advances for human flourishing and equal potential for dangerous or controversial uses, but because they bring forth new complex human interactions and choices that affect both individuals and society.

Legal application of 'old' rules to 'new' technology, in a multitude of contexts or situations that were not predicted by the legislator, generates a variety of possible interpretations of these rules and the unwelcome situation of legal uncertainty. In this report it will be demonstrated that research, clinical and (eventually) commercial non-medical uses of human genome editing technology are linked to an array of identified benefits, risks, ethical, legal and societal implications (sections 4 and 5). These identified risks, warrant an urgent need to further develop governance models, strengthen and harmonise regulatory frameworks (section 6). There are specific areas where regulatory intervention is necessary and thus constitute an opportunity for harmonisation (or at least approximation) of national laws (section 7). To this effect the report proposes a list of possible legislative measures, regulatory tools and governance principles (section 8) and presents policy options (section 9) and conclusions (section 10).

2. Methodology

The present report aim is to provide a critical contextual legal analysis and comparison of different legislative and regulatory approaches to human genome editing. It includes an overview of international, European and EU frameworks and legislation applicable to human genome editing,

also comparing approaches to genome editing in selected EU Member States and the UK. It discusses legal, ethical and social issues surrounding human genome editing and whether these currently have or lack clear and harmonised solutions.

The methodology includes the following:

- Literature review on ethical, legal and social implications of genome editing;
- Survey of existing relevant legislation at the EU and international level;
- Legal interpretation methods relevant for the jurisdictions surveyed.

2.1. Literature review

Scientific literature was conducted with the purpose of identifying discussions, perspectives and opinions on human genome editing ethical, social and legal aspects. Selected literature pertains to legal science, but also to fields adjacent or related to the understanding and regulation of human genome editing. Literature was selected based on its relevance to the advancement of knowledge in the field.

Recent studies in comparative law and ethics of human genome editing and their respective findings was also used to identify relevant literature sources, including previous work conducted by or with the author participation. These studies have also the advantage of being the result of the combined expertise of cross disciplinary groups with strong interdisciplinary component and involved a number of academic cross-dissemination of knowledge activities (e.g. panel discussions, meetings, seminars, workshops and conferences). Some widely cited works doing comparative law studies using social science methodologies were analysed in detail but partly excluded from the findings, because these contain reported methodologic weaknesses in how national law was reviewed and evaluated, affecting either their accuracy or the ability to confirm results independently (see criticism raised by Baylis et al. 2020).

The literature survey included, both academic literature and the analysis of recent international reports scientific bodies (The national academies 2020; WHO 2021); opinions and statements issued by national consultative (bio)ethic bodies (Belgium, Denmark, Italy, France, Germany, Spain, Sweden, UK) and the European Group on Ethics (EGE, 2021). The specific national ethics bodies were selected to correspond to the national legal frameworks analysed. A publicly available ethics council report on genome editing was not found for one of these jurisdictions - Portugal.

2.2. Survey of existing relevant legislation at the EU and international level

Analysis of direct legislative and regulatory sources, both at the level of international, European, EU and National jurisdictions. Sources were consulted primarily in the original language they were published, except where resource to translations or indirect sources was necessary due to language barriers. The legislative survey was also supported by analysis and consideration of recent comparative law studies written by legal experts in the concerned jurisdictions. A number of selected jurisdictions were examined (Belgium, Denmark, France, Germany, Italy, Portugal, Spain, Sweden and UK) to exemplify and emphasise the well-known differences in regulation. Selection and presentation of these national jurisdictions was based on signature and ratification (or not) of the Oviedo Convention, since this international treaty, notably its article 13, had an important impact in the normative sphere. It is however, acknowledged that different reasons explain non ratification and thus status towards the Oviedo convention does not necessary reflect in similar regulatory approaches towards genome editing.

2.3. Legal interpretation methodology

Legal documents were examined and interpreted based on conventional applicable rules for legal interpretation – the legal dogmatic method. A method suited to extract the normative meaning of a given provision and apply it to the specific situation – human genome editing. In interpreting international law, the rules of the Vienna Convention on the Law of Treaties were applied, as well as customary norms of legal interpretation codified in Article 38 of the Statute of the International Court of Justice. A teleological legal interpretation method was also used to interpret EU law in accordance with the practice of the Court of Justice of the European Union (CJEU). The selection and interpretation of relevant national laws of the various countries examined experience usual methodologic challenges of comparative law research. Since traditions and legal culture and practices vary a functional critical contextual approach was applied, to find legal sources that execute comparable functions in the regulation of human genome editing, regardless of their formal status or title. Legal norms need to be interpreted in the context of the legal system their function in the context of their systematic insertion and other rules, regulations, court decisions, soft law instruments, legal culture and social conventions. Such need may become a methodology hurdle in comparative studies such as this one. To overcome this known difficulty, conclusions of the analysis of legal sources were compared and supplemented with the opinions of reputed legal scholars in the concerned jurisdiction.

3. Human genome-editing ethical, legal and social implications

The theoretical legal and ethical debate on governance mechanisms for genomic engineering has a long history in Europe. As will be examined, many of the discussions concerning human genome editing have revolved around prohibitions of eugenics. As such, the regulation of genome editing focuses mostly on this aspect, particularly visible in the context of assisted reproductive technologies and *human enhancement*. This section presents a non-exhaustive review of issues concerning the ethical, legal and social implications of human genome editing previously raised in the literature, organised by groups of topics with legal and regulatory relevance.

3.1. Narratives, metaphors, concepts, and their use for regulatory purposes

Hereditary editing in humans is by far the application of genome editing technology that has generated the most controversy and attention from both regulators and research community. Germline modifications are often linked to existential risks for humanity as a species and as a tool for eugenic policies, programmes and trends. From fears of state-created programmes to *breed* perfect soldiers and Olympic athletes, to employer and school sponsored cognitive enhancement programmes and parents seeking 'designer babies' to match their expectations of a perfect child (Greely, 2019).

Popular culture is ripe with science fiction dystopic and utopic visions of future widespread use of genome interventions. Terminology employed (Lakoff & Johnson, 2008) and the metaphors used (O'Keefe et al, 2015; Steen, Reijnierse & Burgers, 2014) to communicate and disseminate technology and to discuss the related ethical, social and legal implications of genome editing are relevant in so far as these create narratives that frame and indirectly steer the direction of debates (Nordberg et al 2018; Nordberg et al 2020a, EGE 2020; McLeod & Nerlich, 2017).

Legal reasoning must often distance itself both from popular narratives, and some philosophical or sociological categorisations and characterisations that are not helpful in the legal context (Nordberg et al, 2018). Legal instruments need to create and rely on their own legal-technical definitions,

sufficiently general and abstract to ensure respect for equality of treatment, and sufficiently clear and determinable to respect the principle of legality and legal certainty (Nordberg, 2017).

3.2. Moral and legal status of the embryo

The future development of genome editing technologies for clinical uses in assisted reproduction techniques would necessarily require considerable germline research in human embryos and the creation and destruction of such embryos. Advancing scientific knowledge on the safety of human germline editing, thus implies conducting research activities that are in themselves ethically controversial, hurt religious beliefs and generate strong opposing currents of opinion (Annas et al., 1996; Outka, 2002; FitzPatrick, 2003; Lanphier et al, 2015; Baltimore et al., 2015; Savulesco et al, 2015; National academies, 2020; WHO, 2021).

Due to the general lack of consensus on the moral and legal status of the embryo, the creation and/or use of embryos and stem cells for research purposes is also regulated differently in EU Member States, with some jurisdiction being very restrictive (Slokenberga et al, 2019; see also below section 6).

Furthermore, in Europe, patents will not be granted to any inventions, including genome editing treatments, whose research activities implied at some point embryo destruction, due to the interpretation of the CJEU in *Brüstle v Greenpeace* (Case C-34/10) concerning the EU concept of embryo for patentability purposes and the related patentability exception (Nordberg & Minssen, 2016; Sterckx & Cockbain, 2012; Plomer, 2012; Plomer & Anderman, 2009). Given the relevance that the pharmaceutical and biomedical industry attaches to patents as incentive mechanism for investments in research, this remains an area requiring attention (Nordberg, 2020).

3.3. Disability and vulnerability

Genome editing treatments intended to prevent manifestation of serious diseases and severe disabilities and/or their transmission to future generation offer great hope and are welcome by the rare disease community (Kleiderman & Stedman, 2020). However, at the same time there are concerns that such may result in increased discrimination and stigmatisation (Wilkinson, 2010), causing emotional suffering to affected individuals and communities (Boardman 2019; Barter et al. 2017), an erosion of rights to social protection, community support and a reprocess in developing inclusiveness as a normative value (The Nuffield Council on Bioethics 2018; Boardman & Hale 2018).

The debate is not entirely new, the availability of pre-implantation followed by de-selection and prenatal diagnosis followed by abortion, seemingly allows a broader array of options for parents to have a healthy child; but these choices involve morally controversial actions and are coupled with social pressure, e.g. parents faced with a Down's syndrome diagnosis being criticised either for terminating the pregnancy, or for deciding to have the child.

Studies and personal accounts show that some persons born with disabilities may evaluate positively their quality of life (Albrecht & Devlieger 1999), be ready to accept a child with the same condition (Henley 2016; Black 2016; Lancaster 2011) or actively seek one (Shanghavi, 2006; Baruch et al, 2008). These individuals and communities regard their conditions as shaping or being an intrinsic part of their individual personhood and collective identity (Boardman et al, 2017; Boardman & Hale, 2018; Boardman et al., 2019) and may be ambivalent towards genome editing since curing their disability might feel equivalent to erasing part of their sense of self – for example a recent study explores perceptions and attitudes of adults with spinal muscular atrophy towards the genome editing based treatment recently introduced in the market (Pacione et al., 2019).

Some preeminent voices argue that the use (germline) genome editing to cure disabling conditions is ethically acceptable or even a moral imperative (Savulescu, 2001; Savulescu et al., 2015; Savulescu

& Singer, 2019). However, this *principle of procreative beneficence* has been opposed (Bennett 2009; Parker, 2005 and 2007) and even the use of assisted reproduction technologies to de-select disability as for long been criticised (Buchanan 1996; Parens & Ash 2000).

There is general agreement that there is need for a broader societal debate on human genome editing. However, recent calls for greater inclusion of the disability community perspectives in genome editing debates (Boardman 2020a) have also been partially met with counterarguments focusing not only on beneficence but the protection of the human dignity of the disabled embryo (de Miguel Beriain, 2020; cfr. Boardman, 2020b).

Notwithstanding, it remains well known in legal circles that medicalisation of personal traits and identities can lead to various forms of discrimination (being sexual orientation a clear example). Medical classifications concerning disease and disability and related legal determinations are fluid having changed considerably in recent history. Meaning that such determinations are not necessarily immune to context and the availability of new genome editing possibilities is part of such context (see also Feeney, & Rakić, 2021).

3.4. Future-generations agency and commodification of the human body

Debates focusing on the agency of present and future generations and a possible effect of commodification and objectification of the human body have a long tradition in the discussions concerning interventions on the human genome. Habermas raised concerns that human intervention would instrumentalise human beings by means of genetic manipulation, and that such interventions would cause a sense of unfreedom for the modified descendants due to (irreversible) determination by third parties and damage the resulting individuals' sense of being the undivided author of their own life (Habermas, 2003).

While on its turn, Sandel adds that such interventions would be the result of (and further foster) moral character flaws in parents as striving for complete control over their children (Sandel, 2007). Other authors focus primarily on autonomy, have objections to some types of interventions based on concerns that such interventions would narrow the options that the person will have in life and negatively impact the prospective child's 'right to an open future' (Feinberg, 1992; Davies, 1997 and 2009).

In recent years, different types of objections have been raised to the above reasoning. For example, it has been counter argued (in the context of genetic enhancement of abilities) that those who object to human intervention on grounds of it restricting autonomy should nevertheless support, or at least not oppose, the improvement (enhancement) of autonomy (Schaefer, Kahane, G. & Savulescu, 2014).

Other authors, offer a different perspective abandoning the abstract discussion on the permissibility of enhancement to refocus the debate in more concrete discussions concerning the right of (unborn) children to benefit from science and to access preventive personalised medicine (Knoppers & Kleiderman, 2019), and on building pathways for responsible and effective regulation based on a framework 'more realistic and effective than a prohibitive model' (Charo, 2019; on a similar line of reasoning see: Isasi, Kleiderman & Knoppers, 2016; Sykora & Caplan, 2017; De Wert et al, 2018).

3.5. Equal access to genome-editing treatments and social justice

In the past 5 years, multiple gene and cell therapy products have been approved in Europe and the United States (US). The drug approval pipeline is expected to grow exponentially in the coming

decade, since currently there are hundreds of gene therapy clinical trials ongoing (High, 2020; Adair et al., 2021).

There are known problems with equitable access to medicines, in particular in ground-breaking pharmaceuticals and medical technology. Given the huge potential of genome editing technologies for curing or preventing diseases that so far have no available treatment, the prevalence of patented technology in the field and ongoing extensive litigation over such patents (Sherkow, 2018), access issues such as exorbitant high pricing are already a reality.

Costs of approved gene therapy treatments, range from USD 373 000 to USD 2.1 million (Adair et al, 2021). Despite industry funded studies claiming that a price tag of USD 2.125 million for the one-time gene therapy for spinal muscular atrophy *onesamnogon abeparvobek* (Zolgensma - Novartis) justifiably reflects the cost of innovation (Dean et al., 2021; Garrison et al., 2021), the barriers to access are evident are clearly linked to the existing incentive structures and regulatory mechanisms applicable to the pharmaceutical industry.

As the Myriad/BRCA-gene patent (breast cancer diagnosis) commercialisation controversy teaches us (Association for Molecular Pathology v. Myriad Genetics, Inc., 569 US 576; Lai, 2015), excessive optimism towards voluntary responsible industry responses to the need for equitable access may lead to disappointing outcomes (Feeney, 2019). There is a growing global need to consider alternatives to patents or additional incentive mechanisms, as well as eventual judicial or even legislative intervention concerning patentability, patent validity and governance principles and structures to foster responsible marketing practices in the pharmaceutical and biomedicine sector.

3.6. Predominance of private governance and democratic legitimacy deficit

Currently there is a lack of clear and specific regulation concerning genome editing. Existing legislation focus primarily on hereditary or germline modification prohibitions (see section 6 below). This situation allows for considerable leeway in the creation of private governance mechanisms, spearheaded by the main owners of the technology and entities that commercialise patented genome editing products (Feeney, Cockbain & Sterckx, 2021).

While private governance initiatives are welcome, there are dangers in lack of legitimacy and erosion of democratic values (Matthews et al, 2021). In the absence of public regulatory mechanisms private governance risks becoming a form of privatised ethical decision-making on a foundational technology — without public debate, stakeholder involvement and democratic accountability (Hilgartner, 2018).

Although most reports, declarations and policy documents point to the need and value of an inclusive debate, and a number of EU funded projects have been focused and reported findings concerning public participation (Kantar, 2019, Hanson, 2020; Orion, 2021) concerns remains on the lack of appropriate structures, methodologies and capability to ensure its implementation (Morrison & de Saille, 2019).

3.7. Ethics dumping in research and cross-border procurement of health and wellness services

Given the variety of governance approaches and lack of harmonisation in legislation between EU Member States, and internationally, there is also a potential for delocalisation of research to more permissible jurisdictions though research collaborations (Nordberg, 2018). Simultaneously, cross-border procurement of products and services through informal (private) channels is a well-known phenomenon that has inclusively been observed concerning genome editing (Schenkelaars, 2010).

Some countries may either have lack of regulation and other governance mechanisms or reduced ability to enforce existing rules (Baylis et al., 2020). In other countries, commentators argue that the explanation resides in internal or external crisis pushing other more urgent issues into the political agenda, as for example Ukraine where there are reported cases of a clinic planning to offer genome editing for enhancement purposes (Knoepfler, 2021). It has also been theorised that in some cases, maintaining ambiguous or permissive regulations could be part of a deliberate political decision (Schroeder et al., 2019) due to a variety of geopolitical and economic interests in research and innovation in genome editing and in maintaining a lucrative medical tourism industry.

3.8. Therapy, preventive medicine, elective interventions (and 'enhancement')

Regulation of genome interventions has long been linked with the permissibility of human enhancement. The topic has been object of attention by legal philosophers, due to its link with the question of eugenics and its (non-)admissibility.

Rawls, although declining to discuss eugenics, asserts that parents will want to ensure their offspring have the best genetic endowment (Rawls, 1999) arguing that by reason of the *difference principle* - unequal distribution is acceptable if it is to the advantage of those who are worst-off (Rawls, 1999 and 2001) - 'greater abilities are a social asset to be used for the common advantage' (Rawls, 1999) and therefore society should take measures to at least 'preserve the general level of natural abilities and to prevent the diffusion of serious defect' (Rawls, 1999).

Along a similar line of reasoning, Buchanan and co-authors postulate that genetic enhancements are morally acceptable and commendable, and interventions to prevent disabilities a moral imperative (Buchanan et al 2000). Dworkin goes further, stating that morality requires society to allow parents to genetically enhance their children to afford them broader life choices and changes of success. (Dworkin, 2000). These arguments endorse all genetic interventions – heritable or not – provided that these have a beneficial purpose or provide an advantage, but still require a legal predetermination of what can be characterised as such.

Opposing these perspectives, Fukuyama views genetic interventions as a threat to liberal democracy due to their ability to alter human nature (Fukuyama, 2002). In his opinion, contrarities or adversities are both caused by our human condition and part of what constitutes humanity. Removing human imperfections may affect human nature and thus the notions of justice, morality and the good life. Therefore, defending that genetic engineering should be regulated restrictively with its admissibility limited to clear therapeutic treatments (Fukuyama, 2002). Habermas, as examined above, offers as main argument against genetic interventions that these deny the child the possibility to, in adult life, be revised by 'critical reappraisal' (*Aufarbeitung*) (Habermas, 2003).

Common to all these arguments is an underlining reliance on the possibility to clearly define and distinguish, using objective and non-arbitrary criteria, between therapy, preventive medicine, elective interventions and human enhancement (see with further references the discussion in Nordberg, 2017). While specific interventions can and should be regulated according to a range of pre-defined legal and ethical criteria. These regulations will face implementation and enforcement difficulties if based on broad and undetermined categories (e.g. enhancement), unless criteria are developed to clearly distinguish between prohibited interventions. For this reason, many reject the therapy/enhancement distinction, criticising its usefulness (Nuffield Council on Bioethics, 2018) and debating the possibility to objectively establish such distinctions (Gouw, 2018; Mikkelsen et al, 2019; Greenbaum & Cabrera (eds), 2020).

3.9. Rule of law, legal, regulatory and governance pluralism and coherence

It has been pointed that the most salient feature of the current regulatory landscape is the lack of solid comprehensive structures of global governance (EGE 2021; National Academies, 2020; WHO, 2021; Baylis et al., 2020; Slokenberga et al, 2019). Regulation of genome editing has so far followed a vertical approach – germline editing has been prohibited and/or restrictive under rules pertaining to assisted reproduction techniques; while somatic interventions (resulting in modifications that may be or not heritable) is approached from a safety perspective under pharmaceutical and medical devices regulatory framework and medical law. However, there are increases calls and initiatives proposing an integrated, collaborative and inclusive horizontal framework (WHO, 2021).

The existence of a multi layered framework of laws and regulations, operating at international, regional, EU and national level is simultaneously cause and consequence of a complex network of legal overlaps and intersections (see section 6 below). Genome editing opens interpretative challenges because often it is not clear, if and how, new uses and situations fit into the legal categories, and operative concepts of the applicable norms, in the process legal coherence is sometimes sacrificed (Brownsword, 2014; Nordberg & Minssen, 2016).

Coherence in law and regulation can be approached for different perspectives and organised in multiple taxonomies, *inter alia* – geographic or inter jurisdictions coherence (e.g. international, European, EU, etc); regarding its type (e.g. substantive or normative); or from an institutional perspective (e.g. actors involved) (Levenbook, 1994; Dworkin, 1986; Raz, 1994). Technology regulation is however highly complex activity involving multiple factors and perspective (see Brownsword, Scotford & Yeung (eds), 2017; Brownsword, 2019).

Coherence between different areas of law and regulation concerning genome editing would ideally contribute to a closer substantive realisation of the principle of legality and increase legal certainty. Indirectly, coherence also fosters good governance, compliance and enforcement. However, on one hand in matters of regulating genome editing where there are a plurality of ethical understandings and social concerns in EU Member States, legal pluralism may well be a necessity. On the other hand, addressing the challenges of complex technology is also a driver for internal pluralism, as different uses of a technology may warrant differentiated regulatory approaches.

3.10. Conclusion

Literary sources analysed offer a vibrant variety of academic discussions, perspectives, and opinions on the ethical, legal and social implications of genome editing. There is an observed tendency for sources to concentrate around topics related to human germline or hereditary genome editing. A noticeable number of publications are devoted to examining how and to what extent prohibitions of eugenics should be enacted, reformed and enforced. This is more acutely visible, in the contexts of assisted reproductive technologies and human enhancement. Opinions range from libertarian and techno-optimistic views on human genome editing as a vector for promoting well-being and moral and physical improvement of humanity, to bio-conservative, human nature inviolability ontological considerations and precautionary approaches to technology. In the middle of the spectrum a broad range of concerns are found, often framed by specific needs of a given group (e.g. disability) and challenges requiring special attention (e.g. accessibility).

4. Governance of human genome editing

Debates on human genome editing have intensified since 2012, when Nobel laureates Jennifer Doudna and Emmanuelle Charpentier and their collaborators published a seminal paper on the CRISPR-Cas9 technology (Doudna & Charpentier, 2012). Genome editing had previously been

possible, but this technological advance opened the door to new technological possibilities and applications.

In April 2015, Chinese scientists announced the use of gene-editing technology (Liang et al., 2015). The authors of the study stressed that the experiments were conducted in unviable, not intended to be implanted, human embryos and concluded that there was a need to further improve the fidelity and specificity of the CRISPR-Cas9 tool before any clinical applications. The announcement of this research, prohibited in many jurisdictions, was a wakeup call and sparked strong reactions in the scientific community. Soon after, two distinct groups of prominent scientists proposed a worldwide voluntary moratorium on germline genome editing in humans as 'an effective way to discourage human germline modification and raise public awareness' (Lanphier et al., 2015) and a way to prevent such activities in 'those countries with lax jurisdictions where it might be permitted [...], while societal, environmental, and ethical implications of such activity are discussed among scientific and governmental organisations' (Baltimore et al., 2015).

In Europe, national ethics councils assume a leading role in the debate human genome editing governance of debate. Early on, several ethics councils called for international regulation and warned about the need to include ethical principles (see below section 5.3). The European Academies Science Advisory Council, issued a report addressing both human, plant and animal genome editing (ESAC, 2017).

While in the USA, the *Committee on Human Gene Editing: Scientific, Medical, and Ethical Considerations* (established by the National Academy of Sciences; National Academy of Medicine; and National Academies of Sciences, Engineering, and Medicine) published a preliminary report on human genome editing concluding *inter alia* that 'heritable germline genome editing trials must be approached with caution, but caution does not mean they must be prohibited' (NASEM, 2017).

Despite the early warnings, the scientific community was still taken by surprise and shocked when on 25 November 2018, He Jiankui, then a researcher in China, publicly announced he had employed CRISPR-Cas9 technology to edit embryos and that the first genome-edited twin babies had been born (Cyranski & Ledford, 2018; Lovell-Badge, 2019). Since then, rumours of an eventual future support from public institutions in Russia have raised the fear of more such experiences (Kravchenko, 2019).

The announcement of He's experiment immediately led to a storm of criticism in the international scientific, bioethics and legal scholars' community (Charo, 2019; Krimsky 2019; Kleiderman & Ogbogu, 2019; Greely, 2019). Shortly after, scientists, ethicists and legal scholars called for a global observatory on genome editing (Jasanoff & Hurlbut 2018), which was widely supported by the academic community.

A joint statement by the Nuffield Council on Bioethics, the German Ethics Council and the French National Advisory Committee on Ethics in life sciences and health on the ethics of heritable human genome editing called on 'all jurisdictions to bring heritable genome editing unambiguously within the control of relevant public authorities and to make its abuse subject to appropriate sanction' (Bioethics Councils, 2020). While The National Academy of Sciences, Engineering, and Medicine (NASEM), the Chinese Academies of Science, and the Royal Society of the United Kingdom ('the Academies') assembled a commission tasked with developing a framework for the assessment of potential clinical applications of human germline editing.

Also, in the aftermath of this unethical experiment with human germline editing, the World Health Organisation (WHO) established an Expert Advisory Committee on Developing Global Standards for Governance and Oversight of Human Genome Editing. The mandate of the WHO Expert Advisory Committee was broader than the Academies scientific group, since it included governance issues of all types of human genome editing, including somatic/non-heritable.

This section presents an overview analysis of these reports and opinions addressing the ethics and governance of human genome editing, with a view to identify commonalities, divergences and guiding principles for legal and regulatory interventions, which will be presented in sections 7 and 8.

4.1. National Academies report on Heritable Human Genome Editing

As mentioned above, in the aftermath of He's unethical experiment with human germline editing, the US National Academy of Sciences, Engineering, and Medicine (NASEM), the Chinese Academies of Science, and the Royal Society of the United Kingdom (National Academies) assembled a commission tasked with developing a framework for the assessment of potential clinical applications of Heritable Human Genome Editing (HHGE). The commission was composed of 18 members, originating from 10 nations and combining expertise in genome editing technology; human genetics and genomics; psychology; reproductive, paediatric, and adult medicine; regulatory science; bioethics, and international law. The commission was tasked with defining specific criteria and standards necessary before HHGE could be considered for clinical use. Meaning that there is a clear initial standpoint of neutrality regarding either an absolute prohibition of all germline editing or possibly allowing its use for therapeutic applications. The final Report 'Heritable Human Genome Editing' released in September 2020 (National Academies, 2020), was also intended as a tool to inform the work of the WHO Expert Advisory Committee, at the time still ongoing (National Academies News Release, 2020).

The National Academies mandate was focused on addressing scientific considerations needed to inform broader societal decision making and thus it does not make statements on whether safe and efficient uses of HHGE should be allowed, nor does it evaluate technology uses in light of existing legal and ethical frameworks. While acknowledging that societal and ethical issues may need to be further addressed, these are only analysed only if inextricably linked to technical, scientific, medical, and regulatory requirements. These are the main focus of the report that has as main analytic objectives to: (1) determine if the safety and efficacy of genome editing methodologies and associated assisted reproductive technologies (ARTs) are or could be sufficiently well developed to permit responsible clinical use; (2) identify most developed potential applications of HHGE and elaborate on the elements of a responsible clinical translational pathway; (3) additionally the report seeks to elaborate national and international mechanisms for appropriate scientific governance (National Academies, 2020).

The report identifies initial potential uses of HHGE and argues that, if allowed, HHGE should be limited to the prevention of 'serious monogenic diseases, which result from the mutation of one or both copies of a single gene — for example, cystic fibrosis, thalassemia, sickle cell anaemia, and Tay-Sachs disease' (Annex Table 1, Policy options 1 to 4). It recognises that in such cases, HHGE could represent an important option for prospective parents with a known risk of transmitting a genetic disease to have a genetically-related child (commonly known as biological child) without that disease and its associated morbidity and mortality, but advises that such option should only be considered in very restrictive circumstances. The report proposes strict medical requirements for HHGE use, these however do not sufficiently address the individual patients perspective, namely the physical, psychological and moral impact linked to the recommended exams, procedures, including potentially redundant embryo creation and destruction (Annex Table 1, Recommendation 4).

Since it is outside of their mandate, the National Academies report does not make normative considerations concerning the weight of individual reproductive choices versus societal considerations. Nor takes into account public health goals of treatment and eradication of genetic transmitted diseases. The proposed clinical pathway also relies on the existence of pre-clinical knowledge and safety evidence, which would necessarily require the creation and posterior

destruction of a 'significant cohort of edited human embryos' (Annex Table 1, Recommendation 5). While recognising the existence of ethical objections and legal constraints, the report leaves open a normative evaluation of their proposals. Likewise, the national Academies report proposes clinical evaluation plans to evaluate human embryos prior to transfer and subsequent long-term monitoring of outcomes, e.g. monitoring resulting pregnancies and long-term follow-up of resulting children and adults (Annex Table 1, Recommendation 6). Informed consent and availability of genetic counselling are mentioned as important, but the different aspects and consequences of patient agency decisions are not considered. Furthermore, it does not discuss policy options concerning accessibility and availability of medical services related to the proposed life-long clinical monitoring. (National Academies, 2020, pp. 135-138).

Finally, a very important recommendation of the National Academies is that an 'International Scientific Advisory Panel' (ISAP) should be established (Annex Table 1, Recommendation 9). The ISAP should be composed of independent diverse and multidisciplinary experts and be tasked with monitoring and assessment of scientific and clinical developments (National Academies, 2020, pp.158-165). Additional international mechanisms are also recommended for further uses of HHGE (Annex Table 1, Recommendations 10 and 11).

4.2. WHO Expert Advisory Committee on Developing Global Standards for Governance and Oversight of Human Genome Editing Report

In December 2018, the WHO established an Expert Advisory Committee on Developing Global Standards for Governance and Oversight of Human Genome Editing (Expert Advisory Committee), intended to be independent, global and multidisciplinary, tasked with examining the scientific, ethical, social and legal challenges associated with human genome editing, addressing both somatic and germline.

The Expert Advisory Committee objective was to advise and make recommendations on appropriate institutional, national, regional and global governance mechanisms for human genome editing (WHO/SCI/RFH/2019.01). In its first meeting, the Committee agreed with the previously expressed calls for a moratorium, concluding that 'it would be irresponsible at this time for anyone to proceed with clinical applications of human germline genome editing'.

The result of the Expert Advisory Committee's two years of research, consultations and deliberations was released in July 2021 in the form of two documents: (1) a governance framework on human genome editing (WHO, 2021) and, (2) recommendations of the Committee (WHO, 2021a). In addition, a position paper on human genome editing provided a summary of these two publications (WHO, 2021b).

For methodological purposes the expert committee characterised and distinguishes between somatic, germline and heritable genome editing and the recommendations are divided into nine areas: (1) Leadership by the WHO and its Director-General; (2) International collaboration for effective governance and oversight; (3) Human genome editing registries; (4) International research and medical travel; (5) Illegal, unregistered, unethical or unsafe research and other activities; (6) Intellectual property; (7) Education, engagement and empowerment; (8) Ethical values and principles for use by WHO and (9) Review of the recommendations every three years (Annex Table 2).

Unlike the National Academies report that focuses on clinical pathways of a medical-technical nature, the Expert Advisory Committee recommendations concern actionable governance initiatives. These are recommended to be either initiated or further developed by the WHO leadership and the various internal institutional organs and departments, in collaboration with other international institutions and national authorities (WHO, 2021a).

Simultaneously, the Expert Advisory Committee developed a 'Governance Framework' (WHO, 2021). It is a document informed by previous reports on genome editing issues by national ethics committees (including some of the below analysed in section 5.3) as well as the national academies report (see above section 5.1).

Unlike the recommendations, the governance framework is not only directed to the WHO institutional activities but has the broader goal 'to help those tasked with strengthening oversight measures, regardless of whether this is at the international, regional, national or institutional level' (WHO, 2021, p.1).

The proposed framework does not put forward differentiated principles concerning different types of genome editing but focuses simultaneously on all types of genome editing. This is explained because the Expert Advisory Committee initial mandate covers both somatic, germline and heritable human genome editing, but also due to interdependencies between these categories - for example it is referred that somatic interventions may result in heritable changes, even when such is not the goal of the procedure (WHO, 2021, p.16). The Governance Framework identifies a series of identified procedural and substantive values and principles to inform both how and what decisions are made (Annex Table 3). These are divided into:

- (1) *Ethical values and principles and corresponding commitments to inform how decisions are made:* 'Openness, transparency, honesty and accountability'; 'Responsible regulatory stewardship'; 'Responsible stewardship of science' and; 'Responsible stewardship of research resources'.
- (2) *Ethical values and principles and corresponding commitments, to inform what decisions are made:* 'Inclusiveness', 'Caution', 'Fairness', 'Social justice', 'Non-discrimination', 'Equal moral worth', 'Respect for persons', 'Solidarity', and 'Global health justice'.

Many of these principles can easily be related to corresponding fundamental principles of International and EU law and as such are directly or indirectly and to a large extent already part of the existing legal and regulatory framework applicable in EU Member States (see below section 6).

An important and interesting feature of this proposed framework is that it developed and explored five specific special challenges: (1) postnatal somatic human genome editing; (2) prenatal (in utero) somatic human genome editing; (3) heritable human genome editing; (4) human epigenetic editing; and (5) enhancement (WHO, 2021, part 3). For each, challenge the Governance Framework identifies and explores a series of questions that should be considered when reviewing or creating oversight measures (WHO, 2021, part 3).

The Governance Framework also presents a list of possible governance tools (defined as 'Declarations, treaties, conventions, legislation and regulations'; 'Judicial rulings'; 'Ministerial decrees'; 'Conditions on research funding', 'Moratoria' 'Accreditation, registration or licensing', 'National science and medicine societies and institutions', 'Patents and licences', 'Professional self-regulation', 'Public advocacy and activism', 'Research ethics guidelines and research ethics review', 'Collaboration with publishers and conference organisers', 'Education and training of researchers and clinicians'.

There is some overlap in categories, and it is recognised that these are to be used cumulatively or alternatively depending on the scope and nature of the institutions (WHO, 2021, part 4). Additionally, the Governance Framework also explores a series of seven mostly hypothetical, but realistic scenarios used as examples on how to apply the framework (WHO, 2021, part 5). These were object of specific public consultation/call for opinions.

Overall, the report is very comprehensive, and even if the committee mandate was restricted to those governance aspects in the sphere of institutional activity of the WHO, it approaches also important related topics such as intellectual property and patent governance in the health sector putting clear emphasis in collaboration with other international organisations, such as the World

Intellectual property organisation (WIPO) and World Trade Organisation (WTO).

4.3. National Ethics Councils' reports and statements

In recent years, several European national (bio)ethics councils have issued guidance and statements on genome editing (e.g. Belgium Advisory Committee on Bioethics, 2005; Swedish National Council of Medical Ethics, 2015 and 2018; Danish Council on Ethics, 2016; Nuffield Council on Bioethics, 2016 and 2018; German Ethics Council, 2017 and 2019; Italian Committee for Bioethics, 2017; French National Advisory Committee on Ethics in life sciences and health, 2019, and the Spanish Bioethics Committee, 2019). These are analysed in this section, and their main conclusions and recommendations presented by chronological order.

The Belgium Advisory Committee on Bioethics issued its opinion on genome editing before the advances brought by CRISPR-Cas9 technologies. It stands out as generally more positive to germline and non-therapeutic interventions (Belgium Advisory Committee on Bioethics, 2005). The opinion includes a comprehensive, historical account of the evolution of genetics, associated concepts, and scientific state of the art. The historical overview of genetics distinguishes according to mechanisms of action between 'Negative eugenics by the selection of embryos and/or foetus' and 'Positive eugenics by active intervention in the human germ cell line'. It considers both somatic gene modification and germinal gene modification (Belgium Advisory Committee on Bioethics, Ch III and IV) and explores both the arguments of 'bioproggressives' and of 'bioconservatives' with respect to the modification of the human genome.

The conclusions and recommendations focus on 'the therapeutic or enhancement/optimising modification of the somatic or germinal genome' (p. 38). Concerning somatic modifications, the committee observes that, at that time, there had not been any data suggesting successful clinical or other applications. Concerning somatic modifications, the opinion emphasises that previous opinions on human experimentation and ethics approval will equally apply to genome editing. Regarding 'enhancement/optimising gene modification for non-pathological properties', it stresses the importance of a social debate 'to evaluate the feasibility, specificity and opportunities of genetic modification for enhancement', including attention to 'the social and psychological consequences of any applications' (Belgium Advisory Committee on Bioethics, p. 38).

Concerning germline editing, the Belgian Committee found three separate visions or standpoints among its members:

The first group argues that germline editing must be decided case by case depending on the context and the characteristics of the intervention. They consider that if 'a reliable and relatively simple genetic modification technique is available, the consequences of not taking action are just as great as taking any action' and that genome interventions will contribute to the reduction of some social inequalities.

The second group proposes that ethical discussions should concentrate on questions of 'access to new, therapeutic therapies, the transparency of the research and the psychosocial manipulation that may be applicable'. Also raising the question of the place of a genetic disability in society, and how and by whom should be decided 'what "a normal person" is' and what may constitute a genetic improvement.

The third and last group does not see urgent need to address the matter and advocates 'cautious and open progressiveness with respect to scientific and social progress but do acknowledge the risks and advantages involved' (Belgium Advisory Committee on Bioethics, pp. 39-40).

The Swedish National Council of Medical Ethics (SMER) initial conclusions were that optimism was warranted toward the possibilities offered for somatic therapy. It reminded that experiments that introduce inheritable gene modifications are forbidden by law and further advises caution to the

research community, citing unknown risks and other methods available to avoid serious inheritable diseases – preimplantation genetic diagnosis, gametes donation and adoption. The council also encourages a broad societal debate on these issues (SMER, 2015). In 2018 SMER issued a statement concerning the birth of genome edited children, announcing a request for a parliamentary investigation on developing a policy for genome editing and possible legislative changes (SMER, 2018).

The Danish Council on Ethics, critically considers 'the most frequent arguments for and against genetic modification of future humans' organised in seven 'ethical themes': (1) weighing the risks; (2) interests of the future child and of the parents; (3) right to an open future (citing Habermas); (4) genetic modification increases inequalities; (5) natural order; (6) biological diversity 1: tolerance and solidarity; and (7) biological diversity 2: standardisation and totalitarianism (Danish Council on Ethics, 2015, pp. 7-11).

Answering the question of whether 'genetic modification of germ cells and fertilised eggs be allowed with the intention of removing susceptibility to disease in future children and their offspring?' the Danish Council issued two opinions.

The majority opinion is that it would be ethically irresponsible to offer genetic modification of future human beings. The main argument is based on safety risks and uncertainty of potential side effects, complemented by the following: (a) genome editing does not respond to urgent serious therapeutic need of an existing person; (b) risk of side effects in future generations; (c) interference with human nature; (d) availability of alternatives – gamete selection or adoption; (e) germline editing narrows the perception of normality and tolerance towards difference; (f) The difficulty of drawing a line between disease and normality and slippery-slope effect.

The minority opinion argues that there is no ethical difference between treating a child for a given disease after or before birth, as such decisions are always a matter of balancing the risks, potential benefits, and alternatives (Danish Council on Ethics 2015, p. 11-12).

The Italian Committee for Bioethics stresses the importance of an ample public dialogue conducted on various perspectives: scientific, ethics and social. It recommends that public debate takes into account both issues relating to efficacy and safety, but also, the ethical implications of the introduction of genetic modifications potentially transmissible to future generations and the need to find areas of shared international consensus. In this regard, proposing that research continues to be conducted in vitro and/or using animal models.

Furthermore, the Italian Committee for Bioethics It considers ethically acceptable and desirable a strong promotion of research on human somatic cells editing, in accordance with existing research ethics rules. IT considers ethically unjustifiable experimentation on gametes intended for conception and human embryos intended for implantation and supports a call for an international moratorium.

Regarding in vitro research on gametes and embryos not intended for implantation the committee is divided: some members believe that the moratorium against clinical research should not extend to basic in vitro research to avoid completely blocking the development of the technology; while a second group argues that research is currently not justified since it is not possible to verify the results of genome editing on embryos in vitro in terms of its efficacy and safety, given that these can only be evaluated after birth (Italian Committee for Bioethics, 2017, pp. 22-23).

The Spanish Bioethics Committee (CBE) issued a declaration in 2019. It starts by stressing that germline editing generally raises serious conflicts and problems not only scientific but also ethic and social. It adds that genome editing offers great hope to treat genetic based diseases, but the techniques are not safe enough for clinical use. The CBE emphasises that decisions to apply genome editing techniques and corresponding therapies can never be object of sole private initiatives and

that the use of genome editing with purposes, direct or indirectly, of enhancement (as reported in the He experiment) is absolutely reproachable and inadmissible. It considers that the United Nations Educational, Scientific and Cultural Organisation (UNESCO) declarations and the Oviedo Convention show universal consensus on this matter. Finally, it appeals to the scientific community and society in general to ensure that the use of these techniques will be subject to respect for the dignity and equality of all human beings, and to the principles of responsibility, caution and safety (CBE, 2019).

In May 2020, the Nuffield Council on Bioethics, the German Ethics Council and the French National Advisory Committee on Ethics in Life Sciences and Health (CCNE) made a joint statement on the ethics of heritable human genome editing (Bioethics Councils, 2020). This joint statement has as background previously published reports by each of the supra mentioned ethic councils, and punctuates that, although the three councils made different recommendations, these are to be seen as complementary and inform on what appropriate ethical principles should be taken into account and the role they should play (Bioethics Councils, 2020).

Primarily, the Bioethics Councils emphasise that it is of fundamental importance 'that any ethically permissible application should not increase disadvantage, discrimination or division in society (the principle of solidarity and social justice)' (Bioethics councils, 2020). The Nuffield Council further proposes the principle that any intervention should be consistent with the welfare of the future person, while the French and German councils agree on putting considerable focus on the ethical concepts of non-maleficence and beneficence. In addition, the German Council highlights the need to consider the ethical concepts of human dignity, protection of life and integrity, freedom, naturalness and responsibility (Bioethics councils, 2020).

An important feature of this joint statement and of the prior supporting reports is that all three councils find that the clinical application of heritable genome editing could be morally permissible in certain circumstances. It is punctuated that the ethical councils do not 'consider the human germline categorically inviolable' (Bioethics councils, 2020, p. 3). Namely, there is agreement that heritable genome editing could be acceptable to prevent the intergenerational transmission of serious hereditary disorders.

There are, however, national differences in the ethical evaluation of specific applications of genome editing. The French council maintains a complete opposition to 'enhancement' applications, while the German council opts by an assessment of such applications on a case-by-case basis, and the Nuffield Council (UK) does not consider useful a categorical distinction (between therapy and enhancement) and instead punctuates that assessment must take into account the interests and responsibilities of those affected in a given sociotechnical context.

In conclusion the topics debates, approaches and opinions of national ethical bodies in Europe, show commonalities but also a plurality of visions, discourses and arguments, sometimes to the point that even internally unanimity is not possible and minority opinions or currents of reasoning are reported. Demonstrating just how complex it is to develop generally accepted European ethical principles for human genome editing.

4.4. European Group on Ethics in Science and New Technologies (EGE) Opinion

The European Group on Ethics in Science and New Technologies (EGE) is an independent advisory body of the President of the European Commission and evaluates the ethical aspects of science and emerging technologies (Commission Decision (EU) 2021/156).

The EGE recently issued a comprehensive opinion on genome editing, focusing not only on human genome editing, but also covering animal, plants and gene drives (EGE Opinion 32, 2021), following up on an earlier 'Statement on Gene Editing', issued in January 2016 (EGE, 2016).

The EGE makes an overview analysis of ethical issues raised by genome editing technologies, concluding with three common recommendations covering 'overarching matters and concerns', and a series of specific recommendations on each type of genome editing -human, animal, plant or gene drive (EGE Opinion 32, 2021 p. 86). This section summarises the main features of the recommendations applicable to human genome editing:

Common recommendations

- (1) *Foster broad and inclusive societal deliberation on genome editing in all fields of application and with a global scope;*
- (2) *Avoid narrow conceptualisations to frame debates about the ethics and governance of genome editing.*

This recommendation includes a call to 'extend the scope of analysis and debate to underlying concepts and approaches,' since 'traditional dichotomies and divisions, such as those between somatic and germline genome editing, between therapy, prevention and enhancement, or between basic, translational and clinical research can [...] constitute artificial, meaningless or misleading boundaries';

- (3) *Develop international guidelines and strengthen national, regional and global governance tools.*

In this regard, the EGE highlights the need and recommends the establishment of regulatory oversight for 'do-it-yourself' (DIY) genome editing tools (EGE Opinion 32, 2021, p. 87).

Specific recommendations concerning human genome editing

- (1) *Engage in global governance initiatives and create a platform for information sharing and inclusive debate on germline genome editing.*

The EGE considers important that the EU participates in global governance mechanisms with a goal to 'guarantee that heritable human genome editing is not prematurely clinically applied and is not applied for purposes other than against serious diseases that cannot be prevented or treated otherwise'. Cumulatively, it also advises the creation of a European Platform on germline editing for fostering information sharing, public debate and awareness (EGE Opinion 32, 2021, pp. 86-87).

- (2) *Establish a public registry for research on germline genome editing*

The EGE believes that transparency and evidence-based information are of utmost importance to foster an inclusive societal debate. To support such debate, it recommends the establishment of a European and/or global registry for germline genome editing. The registry could be part of the above-proposed European Platform and should cooperate with the global registry for human genome editing established by the WHO. The registry should be publicly accessible to ensure transparency and each entry should be subject to prior ethical approval and compliance with legal requirements (EGE Opinion 32, 2021, p. 87).

- (3) *Protect social justice, diversity and equality*

The EGE stresses the values of protecting human dignity, identity, diversity, equality, social justice and solidarity, urging the EU to proactively develop safeguards 'against enhancement or de-enhancement of traits and to ensure that investments in research on germline genome editing have the purpose of protecting health' (EGE Opinion 32, 2021 p. 87).

The EGE also considers that the use of categorisation of technologies as a tool for ethical evaluation requires the development of guidelines capable of allowing research ethics committees to distinguish between regulatory relevant categories such as 'the definition of technologies and applications of genome editing to be considered as preventive, diagnostic or therapeutic, and those that are to be considered as 'human enhancement' (EGE Opinion 32, 2021, p. 87).

Access to new therapies based on somatic genome editing is also pointed as a concern, and the EGE urges EU institutions to ensure that such access is guided by the principle of social justice and without discrimination (EGE Opinion 32, 2021, pp. 87-88).

(4) *Ensure adequate competencies in expert bodies*

It is considered 'important to widen the basis of expertise and broaden what counts as relevant knowledge at the level of expert committees' and ensure adequate training. The EGE expresses concern with and advises action to prevent 'ethics dumping' through international research collaborations, meaning the delocalisation of research to locations with more permissible regulations and research ethics standards (EGE Opinion 32, 2021 p. 88).

The EGE opinion on genome editing offers a comprehensive and deep ethical reasoning on genome editing. In similarity to other reports, the EGE Opinion also advises against using some categorisations common in ethics literature for regulatory purposes (heritable ν non-heritable; somatic ν germline, enhancement ν therapy). Particularly where such categories are known to be extremely difficult to define with precision in scientific, ethical, and legal terms, and/or are also charged with historical and ethical valuation. However, regardless of this warning, in its recommendations on concrete actions the EGE recommends mostly actions concerning monitoring and regulation targeting germline editing and enhancement as a category.

4.5. Conclusion

The current analysis revealed that the ethics and scientific community, represented by a broad range of disciplines connected with medicine, health care and its regulation either through ethics or regulation, has been strongly invested in the discussion of genome editing, and that there is a broad consensus that regulation and governance mechanisms and frameworks are necessary.

The ethical, legal and social implications and relevant aspects of human genome editing are usually divided in two major blocs, depending on whether the intervention is restricted to the patient or also affects descendants. Somatic interventions are considered from a perspective of medical and health law and regulatory approval of medical and pharmaceutical products for human use. Interventions on the human germline are, on the other hand, considered to pose global and broader risks to humanity and civilisation.

However, such traditional divide, that has so far also been present in the legislative and regulatory framework, has recently been bridged in most above-mentioned reports. It has been widely recognised that scientific advances in genetic knowledge and genome editing technology imply that each intervention risks and benefits requires a deeper consideration depending on a complex number of factors, medical, ethical, and social that cannot be simply reduced to whether an intervention provokes or not hereditary modifications.

5. Legal and regulatory framework applicable to genome editing

A panorama picture of the current legislative and regulatory framework applicable to genetic interventions presents several intertwined lawyers of international and national law and includes a variety of legal instruments ranging from national legislation with direct-enforcing mechanisms to international general principles and recommendations.

UNESCO has put forward general principles applicable to genetic innovation and interventions. Similar principles have been further developed in the Convention on Human Rights and Biomedicine (Oviedo Convention), by the Council of Europe, an organisation that includes most of

the EU countries, but this convention, although very influential, has not been ratified by all EU Member States.

The EU has not directly regulated genome editing. However, it has produced several legislative instruments that are applicable to this technology and contribute to a certain degree of EU internal legal harmonisation – e.g. Biotechnology Directive, Clinical Trials Directive/Regulation, research ethics rules, etc.

Despite these efforts, as will be illustrated in this section, considerable divergence exists between national regulations determining how genome editing tools can be used in clinical practice, as well as considerable diversity of legal interpretation of the legal framework.

5.1. International Law

Historically, domestic legislators and adjudicators have transposed and interpreted international law norms and principles with considerable variation. Something that is particularly visible concerning national standards for the effective realisation of human rights.

Under the Vienna Convention on the Law of Treaties (VCLT, 1980), *pact sunt servanda* principle, international treaties and conventions in force are binding and must be performed in good faith by signatory, ratifying or accessing parties. International law is to be received and integrated in the corresponding national legal orders (Article 26, VCLT). National law must respect and be applied in a manner consistent with those obligations. A state may not invoke its internal law as justification for not implementing a treaty (Article 27, VCLT).

The principle of good faith implies that international law principles and norm, should be transposed and applied in practice according to its spirit and not merely as a matter of literal correspondence. Comparative legal history demonstrates that this is extremely difficult to fully achieve. National reception and implementation of international law in most cases obeys to its letter, but not always to its spirit. For example, the intended meaning and harmonisation objectives of a treaty can be partly lost or watered down once these principles are interpreted and enforced according to a pluralism of local legal traditions, cultural and political contexts.

Humanitarian Law was established to crystallise the fundamental ethical-normative principles that should guide all legislative activity and constitute a minimum content of all fundamental and constitutional laws. Human rights norms provide guidance and serve as platforms for development and harmonisation of regional and national legislation and jurisprudence. In this sense constituting an international umbrella framework for regulation. UNESCO has developed three declarations relevant to genetic technology. However, these instruments are not binding documents and lack enforceability. As a rule, declarations do not create legal obligations for States that adopt them, their function and legal value is one of establishing guidance and ethical-legal orientation though normative principles. Creating, instead political and moral obligations to UN Member States to conform to and reflect these principles in national and supranational legislation.

5.1.1. UNESCO's Universal Declaration on the Human Genome and Human Rights

Adopted in 1997, the *Universal Declaration on the Human Genome and Human Rights* (Human Genome Declaration, 1997) declares that the human genome is a symbolic cultural heritage of humanity:

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. (Article 1, Human Genome Declaration)

This legal principle has influenced and is present and developed in subsequent legal texts. It has also originated vivid debates concerning its interpretation and implementation (Nordberg et al., 2020). The Human Genome Declaration establishes a principle of non-discrimination (Article 6, Human Genome Declaration) and respect for human dignity regardless of genetic characteristics and against any ideology that reduces individuals to such genetic characteristics, linking respect for human dignity to respect for each individual 'uniqueness and diversity' (Article 2, Human Genome Declaration). It recognises both that the human genome by nature evolves and is subject to mutations, and that 'it contains potentialities that are expressed differently according to each individual's natural and social environment including the individual's state of health, living conditions, nutrition and education'. (Article 3, Human Genome Declaration). It further addresses uses of genetic interventions by establishing a principle of prior assessment of potential risks and benefits of both research, treatment or diagnosis affecting an individual's genome, subject to free and informed consent; as well as the right of each individual to decide whether or not they wish to be informed of the results of any genetic examination (Article 5, Human Genome Declaration).

The Human Genome Declaration prohibits practices contrary to human dignity and invites States and competent international organisations to co-operate in identifying such practices and in taking appropriate measure against them. It specifically points out reproductive cloning of human beings as one such practices (Article 11, Human Genome Declaration). It also directs States to 'recognise the value of promoting, at various levels, as appropriate, the establishment of independent, multidisciplinary and pluralist ethics committees to assess the ethical, legal and social issues raised by research on the human genome and its application' (Article 16, Human Genome Declaration).

Although germline editing is not prohibited directly, Article 24 mandates the UNESCO's International Bioethics Committee (IBC) to provide advice regarding 'practices that could be contrary to human dignity', identifying human germ-line interventions as a bench-mark example. This provision clearly signals that germline interventions are considered highly problematic. The wording choice and the use of the verbal form 'could be contrary', implies that determining whether a given germline intervention might offend human dignity could depend on the specific context or at the very least indicates lack of consensus on a total ban. As the IBC later recognised its 2015 Report on Updating Its Reflection on the Human Genome and Human Rights, the constant and fast developments in genetics require continuous reflection and re-interpretation of the principles set in these declarations (IBC, 2015, pp. 127-128).

It is also evident that the Human Genome Declaration is aimed at preventing states from using genetic knowledge and technologies to implement eugenic experiments, programs or discriminatory practices. However, the potential for therapeutic uses of the technology sparked a major point of debate. Eugenic ideologies and practices are a painful and abhorrent historical memory, but there is real danger that genome editing technology will be used in unethical ways. However, the declaration cannot be interpreted as prohibiting access to therapeutic interventions that can cure diseases or prevent pain, suffering and death in families affected by genetic mutations, since such would collide directly with the right to health and right to benefit from science.

5.1.2. UNESCO's International Declaration on Human Genetic Data

The *International Declaration on Human Genetic Data*, adopted in 2003, deals mainly with data protection and privacy issues concerning genetic data. It aims to 'ensure the respect of human dignity and protection of human rights and fundamental freedoms in the collection, processing, use and storage of human genetic data, human proteomic data and of the biological samples' (Article 1, Human Genetic Data Declaration).

It presents the principles of respect for diversity, non-discrimination, non-stigmatisation, and autonomy as being recognised underlying consequences of respecting human dignity (Article 7, Genetic Data Declaration; cf. Article 6, Human Genome declaration; Article 11, Bioethics

Declaration). In this sense, declaring the human genome to be a heritage of humanity should not entail reducing humanity to its biological dimension. The International Declaration on Human Genetic Data re-affirms a broad construction of the concept of personhood as not merely defined by biology and stating that 'a person's identity should not be reduced to genetic characteristics, since it involves complex educational, environmental and personal factors and emotional, social, spiritual, and cultural bonds with others and implies a dimension of freedom' (Article 3, Genetic Data Declaration).

The principle of non-discrimination and non-stigmatisation is of special interest for human genome editing, as it prescribes that the international community should ensure that human genetic data and human proteomic data are not used for purposes that discriminate – e.g. directly or indirectly 'infringing human rights, fundamental freedoms or human dignity of an individual'- or used 'for purposes that lead to the stigmatisation of an individual, a family, a group or communities' (Article 7(a), Genetic Data Declaration). Indirectly, this principle also entails that genetic data, for example 'population-based genetic studies and behavioural genetic studies and their interpretations' (Article 7(b), Genetic Data Declaration), should not be used to identify future disabilities where such might result in discrimination (e.g. in employment or insurance) or violation of human dignity (e.g. using such information to pressure or mandate individuals and families to undergo genome editing therapy or preventive medicine programs).

5.1.3. UNESCO's Universal Declaration on Bioethics and Human Rights

The Universal Declaration on Bioethics and Human Rights, followed in 2005 with the objective to establish a universal framework of principles and procedures that would be used as a guide in the formulation of legislation, policies, rules, and actions in the field of bioethics (Article 2, Bioethics Declaration). An interesting aspect of this Declaration is that it was explicitly directed not only at state actors, as it is typical of public international law, but also at other public or private actors and corporations (Article 2, Bioethics Declaration).

The Bioethics Declaration develops a principle of primacy of individual interests over the interests of science and society (Article 3, Bioethics Declaration; See also Article 10 Human Genome Declaration) further consecrating the principles of maximising benefit and minimising harm to affected individuals, autonomy, informed consent and privacy (Articles 4 to 9, Bioethics Declaration). Clearly aligned with the Helsinki Declaration (World Medical Association, 1964) that establishes self-regulatory medical deontological principles of medical practice and research.

Especially relevant to genome editing is the principle of protection future generations as well as the protection of the environment, the biosphere, and biodiversity (Articles 16 and 17, Bioethics Declaration). In this regard the Bioethics Declaration prescribes that due consideration should be paid to the protection of future generations from 'the impact of life sciences', and namely the impact on their genetic constitution (Article 16, Bioethics Declaration).

All principles in this declaration are to be understood as complementary and interrelated (Article 26, Bioethics Declaration) and thus the principle of primacy of individual interest, mentioned above, frames the entire declaration. In the context of genome editing it allows to interpret other principles including the principle of protection future generations in light of individual rights and to argue for exceptions from prohibitive regulations, based on other principles such as the principles of equality, justice and equity; non-discrimination and non-stigmatisation; respect for cultural diversity and pluralism; solidarity and cooperation; social responsibility and health; and benefit sharing (Articles 10 to 15, Bioethics Declaration). Furthermore, it is of tantamount relevance that the Bioethics Declaration is intended to guide, not only State actors, but also act as a governance guide for corporations and other non-state actors (public or private).

5.1.4. The IBC Report on the Human Genome and Human Rights

In 2015, the IBC released an updated *Report on the Human Genome and Human Rights* (IBC, 2015). Its most important feature is the recommendation of a moratorium on genome editing of the human germline, justified by safety and ethical concerns (para 118, IBC 2015). The IBC Report also issues a number of other final recommendations, namely:

- (1) The IBC states the importance of global responsibility and governance regarding scientific and technological advances in genomics (para 115, IBC 2015).
- (2) Governments and stakeholders are asked to join forces to avoid leaving for the mechanisms of supply and demand decide the acceptability of technology and its uses.
- (3) The IBC advocates for global standard setting and regulation (para 116, IBC 2015), reinforcing the importance of assuring the involvement of the scientific and bioethics community in a global debate.
- (4) The IBC report also proclaims that the united nation should make normative decisions in this area and that such decisions should be guided and respect a precautionary principle (para 117, IBC 2015).
- (5) Finally, the report points out that health protection and health care applications, including 'precision and personalised medicine, should be considered as content of the fundamental right of every human being to enjoy the highest attainable standard of health', while enhancement techniques or non-medical uses should respect human rights and dignity and obey the precautionary principle (para 122, IBC 2015).

5.2. The Council of Europe Convention on Biomedicine

The Convention on Biomedicine, concluded in 1997 and known as Oviedo Convention is an international treaty elaborated by the Council of Europe, a regional organisation with 47 Member States. The Oviedo Convention has been signed by 34 and ratified by 29 European countries including the majority of EU Member States. In the EU it has not been signed by Austria, Belgium, Germany, and Ireland. Some EU Member States have signed but not yet ratified the treaty – i.e., Italy, Poland, Sweden and The Netherlands. The UK has not signed this treaty (Council of Europe: Chart of signatures and ratifications of Treaty 164).

The Oviedo Convention directly considers the regulation of interventions in the human genome, stating that:

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 (Article 13, Oviedo Convention).

In a literal reading, this norm appears to contain a principle of absolute prohibition of all non-therapeutic and research interventions, and also a prohibition of any modification affecting future generations regardless of their purpose or scope. However, the specific wording and structure of the norm supports a different reading. Legal scholars argue that is possible to interpret this provision as allowing interventions aimed at medical purposes even if this may entail a modification passed on to descendants, due to the used expression 'and only if the aim is not to introduce any modification in the genome of any descendants' (Nordberg et al., 2018). This would be the case of an intervention on the genome whose purpose is to correct a mutation, prevent, treat or even irradiate a severe condition or disease. In such cases the direct aim of the intervention would be therapeutic – to prevent, treat or cure, while the modification of future generations in that family an effect, but not the aim of the intervention.

If we accept the above exposed interpretation, acceptance of the intervention would be a matter of weighting the medical benefits against the risks of the procedure, considering the available

therapeutic alternatives for the individual, and conducted according to medical best practices and medical law rules and regulations concerning high risk procedures.

The explanatory report to the Oviedo Convention, which has interpretative value (para 90, Explanatory report Oviedo convention), clarifies that Article 13 'does not rule out interventions for a somatic purpose which might have unwanted side-effects on the germ cell line', thus making a legal distinction between aim and result of a given intervention (para 92, Explanatory report Oviedo convention). It also punctuates that the protection of the dignity and identity of all human beings is the primary goal and general interpretative guiding principle of the Convention (Article 1, Oviedo Convention). Dignity and identity are here understood as protecting the biological and genetic identity of the species (Article 2, Oviedo Convention) and inspired by the principle of the primacy of the human being (para 22, Explanatory Report Oviedo Convention). Arguably, this principle can be respected even allowing genome-editing interventions where the objective is to prevent or correct genetic mutations, since these can be seen to be by themselves a threat to the integrity and future of human identity (para 92, Explanatory Report Oviedo Convention).

Already in 1982, the Council of Europe (CoE) Recommendation 934 on Genetic Engineering explicitly states that 'the rights to life and to human dignity protected by Articles 2 and 3 of the European Convention on Human Rights imply the right to inherit a genetic pattern which has not been artificially changed' (para 4a, CoE Rec. 934), adding that recognition of such right 'must not impede development of the therapeutic applications of genetic engineering (gene therapy), which holds great promise for the treatment and eradication of certain diseases which are genetically transmitted' (para 4c, CoE Rec.934).

The drafters of the Oviedo Convention were aware that technology development could affect the normative content, and thus debated the possibility for creating exceptions. At the time, concluding that such was premature and thus consistently stressed the need for Article 13 to be reviewed after a certain period of time to avoid precluding future genetic therapies (Preparatory Works Oviedo Convention, p 63-68).

Posterior advances in science and society offer new perspectives to legal interpretation if the relevance of the literal and historic element is tempered with a contextual dynamic legal interpretation. Such is supported by a broad and consistent application of the elements of interpretation of international treaties mentioned in Articles 31 and 32 of the Vienna Convention.

The Committee on Bioethics of the Council of Europe, December 2015 issued a Statement on genome editing technologies (DH-BIO/INF (2015) 13 Final), pointed out that technologic developments new advances justify public debate (Article 28, Oviedo Convention) and therefore agrees to examine issues brought by genome editing. As part of its *Strategic Action Plan on Human Rights and Technologies in Biomedicine (2020-2025)*, the Committee on Bioethics of the Council of Europe decided to examine Article 13 of the Oviedo Convention in the light of developments in genome editing technologies with the objective to evaluate whether there is a need to clarify or amend Article 13. More recently, at its 18th plenary meeting (1-4 June 2021), the Committee on Bioethics of the Council of Europe concluded that 'conditions were not met for a modification of the provisions of Article 13. However, it agreed on the need to provide clarifications, in particular on the terms 'preventive, diagnostic and therapeutic' and to avoid misinterpretation of the applicability of this provision to 'research' (DH-BIO 2021) and announced ongoing work to 'Set up a drafting group' (www.coe.int).

5.3. European Union

This section provides a very short overview and discussion of the existing European Union (EU) legal framework applicable to human genome editing interventions in the EU. A first observation is that currently, there is a lack of specific and comprehensive EU regulation addressing all legal issues

concerning genome editing technologies and interventions (de Miguel Beriain, 2017). This being followed by a second observation that such is not equivalent to a legal vacuum, since general principles and rules are relevant and applicable to a variety of situations and may also be relevant for interventions on the human genome. EU Pharmaceutical Law is composed of a long list of complex legislative instruments (for a full list see EUDRALEX vol 1 to 10) that are applicable also to human genome editing products.

Mentions to interventions in the human genome can be found in a variety of EU instruments, such as the Biotechnology Directive (Directive 98/44/EC); the Clinical Trials Directive/Regulation (Directive 2001/20/EC; to be replaced by the full entry into force of Regulation 536/2014); the regulations on advanced therapy medicinal products (ATMP) (Regulation (EC) No 1394/2007; Directive 2001/83/EC; Regulation (EC) No 726/2004); Directive on investigational medicinal products for human use (Directive 2005/28/EC); to be replaced once the Clinical Trials Regulation entries into force and replaced by Commission Implementing Regulation (EU) 2017/556); the Human Tissues and Cells Directive (Directive 2004/23/EC). Furthermore, outside of the scope of this report, but also relevant, are the data protection rules in the General Data Protection Regulation (Regulation (EU) 2016/679).

The EU legal framework here presented, should be understood within the context of the intersection of legal sources sometimes with an unclear or disputed hierarchical relationship between them, and a complex interface between the EU and national member state respective legislative competences.

5.3.1. EU Charter of Fundamental Rights

The Charter of Fundamental Rights of the European Union (EU Charter 2012) contains so called 'third-generation' fundamental rights relevant to institutions and bodies of the EU and national authorities when developing and interpreting EU law in the field of bioethics and technology regulation. Particularly relevant is Article 3, which establishes an individual right to respect for physical and mental integrity, including in particular in the fields of medicine and biology, 'the prohibition of eugenic practices, in particular those aiming at the selection of persons' and 'the prohibition of the reproductive cloning of human beings' (Article 3, EU Charter).

Article 3 was never meant to address genome editing as a therapeutic option (de Miguel Beriain, 2019). These prohibitions should be read in conjunction with Article 35 that establishes 'the right of access to preventive health care and the right to benefit from medical treatment under the conditions established by national laws and practices' (Article 35, EU Charter). Considered together, the EU Charter does not prohibit all germline or hereditary human genome editing, because therapeutic applications are allowed under the right to preventive health, including the right to health of future or unborn persons.

Somatic human genome editing is to some extent covered by part of the scope of Article 3 of the EU Charter, insofar as it can be used as a tool for eugenic practices, but also here it does not cover all types of non-medically justified somatic procedures, commonly debated as human enhancement. Elective treatments and interventions are a commonly acceptable form of exercising self-determination, autonomy and agency rights, a clear example are cosmetic surgeries.

It is debatable if and to what extent can the concept of eugenics cover free and informed individual choices; if it is only meant at government sponsored programs or if it addresses also private entities such as employers. It is also a matter for debate what type of interventions and treatments (or conjugations thereof) might be qualified as eugenic practices. The CJEU in *Netherlands v European Parliament and Council* (Case C-377/98, at grounds 70 and 78 to 80) made a narrow interpretation of eugenics, as equivalent to practices aiming at the selection of persons and linking it to the concept of crimes against humanity (Article 7(1) (g), Statute of the International Criminal Court). Examples provided refer to 'campaigns for sterilisation, forced pregnancy, compulsory ethnic marriage', supporting a reading that Article 3 of the EU Charter only applies to public authorities and

to widespread or systematic practices.

Even if a broad concept of eugenic practices could be considered under Article 3, as mentioned above Article 35 expressly includes preventive health care under the right to health. The concept of preventive medicine is complex, fluid and deeply connected with technological state of the art and individual circumstances. Any regulatory or governance activity anchored in a prohibition of non-therapeutic genome editing would have to carefully address the complex and delicate interface with the right to health, right to benefit from science and personal autonomy over one's body.

5.3.2. Biotechnology Directive

The Biotechnology Directive (Directive 98/44/EC) clarifies and harmonises certain aspects of patentability of biotechnological inventions. It is intrinsically connected with the European Patent Convention (EPC), a pan-European international treaty establishing the European Patent Organisation (38 Member-states) and an organisation - the European Patent Office (EPO) – responsible for processing, examining and granting grants covering the Contracting States and States that have concluded extension and validation agreements with the EPO. The Biotechnology Directive substantive rules have been incorporated in the EPC implementing rules (Decision of the Administrative Council EPO, OJ EPO 7/1999), ensuring correspondence between European and EU patentability rules.

Patent rights are important incentives to innovation. As such, patent law norms that exclude, prohibit, or limit the ability of inventors to obtain, dispose and enforce patent rights assume an indirect public and private governance function. This governance function is exercised through public governance tools, including for example legal rules on patentability and patentability exclusions, exceptions, and enforcement limitations; but also, through private governance mechanisms, such as licensing agreements, enforcement strategies and technology use policies (Matthews et al., 2021).

Patent rights are not positive rights, but rather provide an entitlement to market exclusivity, meaning an exclusive right to prevent others from using a patented product or process, and from making, offering for sale, selling or importing for these purposes a patented product or a product obtained directly by a patented process (Article 62 EPC, in conjunction with Article 28 TRIPS).

Patents are granted independently of market regulatory approval (Article 4^{quater} Paris Convention; Article 27 (2) TRIPS *in fine*; Article 53 (a) EPC *in fine*). The grant of a patent cannot be refused, nor a patent invalidated merely on the ground that the sale of the patented product or of a product obtained by means of a patented process is subject to legal prohibitions or restrictions. Conversely, refusal of the patent office to grant a patent does not mean that the technology will not be allowed into the market.

Regardless of a technology being patented or not, it is up to the different regulatory authorities to decide, in accordance with existing regulations, whether to allow, restrict or prohibit products or methods and in some cases some possible uses of a given technology. Regulations determine also which uses are permitted, whether the technology can be used by and sold directly to the general public or requires intervention of certified professionals (e.g. prescription medicines), and what safety measures should be in place.

Patent law contains a number of exceptions to patentability, including the 'ordre public' and morality provision (Article 53 (a) EPC and Article 6 Biotechnology Directive). Certain exceptions to patentability function as a public governance mechanism, either by excluding certain inventions from the patent incentive mechanism discouraging investment in research and development of inventions whose commercial exploitation is considered unethical, or by signalling that innovation in certain areas should not be object to private entitlements - e.g. medical method (Article 53(c) EPC) (see with further references Nordberg, 2017a, pp. 82-92). Exceptions act as governance tools also through a pedagogic or market-signalling effect (Long, 2002; Carvalho 2010, pp. 30-47), conveying

that those inventions will not benefit from the market exclusivity conferred by patents, thus signalling the importance of compliance with the core ethical values of society.

Exception to patentability on inventions regarding germline modification

Germline modification patentability is expressly prohibited under the Biotechnology Directive as well as in Article 53 (a) EPC, as clarified in Rule 28(1)(b) of the EPC Implementing Regulations. This norm explicitly excludes 'processes for modifying the germline genetic identity of human beings'. This means that only process claims are expressly covered by the letter of the law. Process claims are 'applicable to all kinds of activities in which the use of some material product for effecting the process is implied' (F-IV, 3., EPO Guidelines for Examination, 2021).

Patent claims on processes for editing disease responsible mutations or repairing the genome through germline modification are an area where the scope of the prohibition is debated. Recital 42 of the Biotechnology Directive states that the germline 'exclusion does not affect inventions for therapeutic or diagnostic purposes which are applied to the human embryo and are useful to it'.

The CJEU in *Brüstle* and *International Stem Cell Corporation* developed a broad interpretation of the legal concept of embryo for patent purposes. Therefore, it has been argued that processes for therapeutic genome editing in any human ovum after fertilisation, e.g. to correct a mutation, should not face objections (Nordberg et al., 2020; Matthews et al., 2021).

However, the academic debate remains, since this norm application to genome editing tools has not been object of clarification by neither the BOA nor the CJEU. Since, in order to avoid challenges, patent activity concerning genome editing has resorted to disclaimers. Through disclaimers, patent owners voluntarily have narrowed down the scope of the patent applications submitted in Europe, excluding germline and thus avoiding litigation.

Exception to patentability on inventions implying uses of human embryos for industrial or commercial purposes.

Under the rules set by the Biotechnology Directive, genome editing inventions may also be excluded from patentability indirectly. Provided that the invention implies the destruction of an embryo or uses stem cells as base material, unless such stem cells lines were obtained from parthenotes. Following the CJEU jurisprudence in *Brüstle*, this limitation applies even in cases where the destruction occurred at an undetermined historical moment and does not form part of the invention concept described in the claims.

General 'ordre public' and morality exception to patentability

Product claims, even if related to germline modification are not mentioned directly in the specific prohibition and as such can only be excluded under the general morality clause and on a case-by-case basis. Likewise, somatic cell interventions, also fall outside the scope of the exception to patentability but in theory can still be denied patentability under the general '*ordre public*' and morality clause. The possibility to patent inventions intended for induced human evolutionary or human enhancement purposes (Nordberg, 2017; Nordberg 2017a), can also possibly be restricted. However, due to the dual use dilemma, in patent law 'a possible immoral use is only to be taken into account if it is specifically considered or at least suggested in the application and can thus be found to constitute an avowed use' (EPO Guidelines, 2021) (G-II, 4.1, and T 866/01).

Governance role of patent licensing practices and mechanisms

The nature of patent rights - exclusionary rights - allows patent holders, individually or in organisations, to make private governance decisions over a patented technology. Genome editing

technology is heavily patented in a complex, ripe with litigation landscape (Matthews et al., 2021, Nordberg et al., 2018, IPSTUDIES, 2020). Patent rights provide a measure of control on how the technology is used. Patent holders directly exploiting their patents decide what type of products will incorporate their patented inventions and what sales channels to use. Right holders can also decide whether to allow third parties to use a patented technology by issuing a license and negotiate licencing terms and conditions. There are different types of licences and licensing strategies.

Exclusive licensing was a common strategy for earlier genome editing patents (Graff & Sherkow, 2020). Patents were at the time owned by a relatively small number of actors who licensed it exclusively to spin-off companies with an exclusive right to sub-license. This practice known as *surrogate licensing* was relatively common in the CRISPR context, where patent holders transferred to surrogate licensing companies' exclusive rights to use patented CRISPR technologies to develop any human therapeutics, targeting any gene on the human genome (Contreras & Sherkow, 2017).

Collaborative licensing refers to licensing agreements negotiated simultaneously by multiple patent holders to license clustered patented technologies through one third party license for a reasonable royalty. In areas where patent ownership is fragmented, collaborative licensing mechanisms are considered useful mechanisms and recently, initiatives have emerged to explore their potential.

There are two main types of collaborative licensing strategies - patent pools and clearing houses (Van Zimmeren, 2011; Minssen, Van Zimmeren & Wested, 2018). In April 2017, MPEG LA (self-described as the world's leading provider of one-stop licenses for standards and other technology platforms) issued an invitation to patent holders to participate in a CRISPR-Cas9 patent pool (O'Reilly/ MPEG LA, 2017). In response, prominent actors in the CRISPR-Cas9 patent landscape - the Broad Institute, the Rockefeller Institute, Harvard University and Massachusetts Institute of Technology - announced the intention to join (GEN, 2017).

However, ongoing litigation between the participants and exclusive licenses granted cast a shadow over the feasibility of such endeavour (Contreras & Sherkow, 2017). MPEG LA has announced the possibility to exclude in the pool licensing conditions authorisation to certain uses of the technology. In theory, such ethical licencing provisions and private initiatives could play a relevant role in human genome editing governance (Guerrini et al., 2017; Sherkow, 2017). However, commentators have highlighted democratic deficits and limitations of such model (McMahon, 2020; Feeney et al., 2021).

In general, patent licensing practices play a significant technology governance role and can have long tail effects, positive and negative, on further research and access to health technology. Licensing and enforcement strategies and practices are already used by relevant actors (companies, universities, research facilities) not only to ensure technology control, but also to foster socially responsible use (Matthews et al., 2021).

Patent licensing operates under the general principle of contractual freedom, where parties are free to decide and negotiate terms. Due to a general absence of legal constraints on licensing practices (besides competition rules), there is in practice a transfer of regulatory power from public (law) to private actors (contracts) at the cost of transparency, accountability and legal certainty. This is certainly an area where further development of governance tools, including regulation, would be beneficial.

5.3.3. Clinical trials and market approval of medicinal products for human use

The testing and market introduction approval of any therapeutic uses of genome editing tools is subject to EU harmonised rules under the Clinical Trials Directive (Directive 2001/20/EC), replaced from 31 January 2022 by the Clinical Trials Regulation (Regulation 536/2014); the regulations on advanced therapy medicinal products (ATMP); and the extensive and complex legal framework governing medicinal products for human use. Clinical Trials are also subject to the governance

principles created by the *Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects*, adopted by the General Assembly of the World Medical Association (Helsinki Declaration 1996) and *ICH guidelines on good clinical practice* (Article 47, Regulation 536/2014).

The requirements and procedures for marketing authorisation, as well as the rules for monitoring authorised products, are primarily laid down in the Community Code Relating to Medicinal Products for Human Use (Directive 2001/83/EC) and in Regulation (EC) No 726/2004 establishing the European Medicines Agency (EMA).

Other relevant legislation includes Directive 2005/28/EC containing inter alia detailed guidelines for good clinical practice and the requirements for authorisation of the manufacturing or importation of gene therapy products and techniques (Article 10 2005/28/EC). This directive is soon to be repealed once the CTR entries into force, but similar rules will remain applicable. Finally, if /when human tissues and cells are used as starting materials for genome editing products, rules concerning the donation, procurement and testing of such tissues and cells are regulated by the Human Tissues and Cells Directive (Directive 2004/23/EC).

Genome editing uses in, for example, human reproductive technology (ART) or advanced therapy medicinal products (ATMPs), including also techniques used in the process, have to be tested in clinical trials to meet the requirements for market authorisation. Article 9(6) of the Clinical Trials Directive (see also articles 4 to 14 in the CTR) prescribes that 'No gene therapy trials may be carried out which result in modifications to the subject's germline genetic identity.' This sentence has also been incorporated in Article 90 of the new EU Regulation on Clinical Trials, which is meant to replace it once it entries into force. This restriction on conducting clinical trials results in an unsurpassable hurdle, making it in practice inviable to obtain market approval for related medical products and therapies, and thus an impediment to commercialisation as a human medicinal product.

The use of the open concept 'genetic identity', also present in the international framework is difficult to implement in practice. Indeed, there is very little guidance to determine what can be concretely considered as the *germline genetic identity* of a given person participating in a human clinical trial as a subject, for example whether it also includes mutations. It also to be determined whether *germline genetic identity* should be constructed as an autonomous concept of EU Law or is a matter of pure factual determination.

The ATMP Regulation 'lays down specific rules concerning the authorisation, supervision and pharmacovigilance of advanced therapy medicinal products' (Article 1, Regulation 1394/2007 ATMP). It is thus mostly concerned with the evaluation of quality, safety and efficiency of advanced therapy medicinal products. The ATMP Regulation is *lex specialis* to Directive on the Community Code relating to Medicinal Products for Human Use (Dir. 2001/83/EC Medicinal Products Code) meaning that it introduces additional and more specific provisions. Neither legislative instrument regulates specifically what possible uses of genome editing products are allowed.

The Medicinal Products Code contains definitions of *gene therapy medicinal product* and *somatic cell therapy medicinal product*, which require that these products are used for treating, preventing or diagnosing a disease (2.1. and 2.2., Part IV, Annex I Directive 2001/83/EC). This implies that the rules prescribed in the Code are only applicable to gene therapy products that have such purposes. Products that cannot be justified as therapeutic (e.g. products with cosmetic or wellness purposes) are outside the scope of this regulatory framework. Another concern is that the current definition of gene therapy medicinal products 'risks excluding molecules which are not manufactured through techniques involving recombination' (Mourby & Morrison, 2020).

The Clinical Trials Directive/Regulation and the specific rules mentioned above concerning ATMPs are only applicable to specific medicinal products, and within the limited context of clinical trials and market authorisation procedures, for example concerning clinical trials involving medicinal products for gene therapy, somatic cell therapy including xenogenic cell therapy and all medicinal products containing genetically-modified organisms. While having a governance effect through

influencing the research community and industry, these regulations do not directly regulate clinical uses of genome editing, nor any uses outside a healthcare setting.

This regulatory framework contains three mechanisms created to ensure that patients in need of urgent care do not have to wait for the long process of marketing approval and that early access can be allowed in specific well justified circumstances. These are: *compassionate use*, *named-patient use*, and specific to ATMP's the *hospital exception*.

Compassionate use was created by Article 83 of Regulation (EC) No 726/2004. The EMA, through the Committee for Medicinal Products for Human Use (CHMP), provides recommendations on how a product should be used and what type of patients may benefit from treatment, but *compassionate use* programmes rules and procedures are determined and implemented by each Member State. *Named-patient basis* are access requests made under the direct responsibility of an attending physician and made on an individual patient basis to obtain medicines directly from manufacturers before market authorisation has been granted.

The *hospital exception* is specific to ATMP's and is applicable to any ATMP 'which is prepared on a non-routine basis according to specific quality standards, and used within the same Member State in a hospital under the exclusive professional responsibility of a medical practitioner, in order to comply with an individual medical prescription for a custom-made product for an individual patient' (Article 3(7) Directive 2001/83, Article 28, ATMP Regulation (EC) 1394/2007). It is up to the competent national authorities to authorise the manufacture of these products. Member states should also ensure that national traceability and pharmacovigilance requirements, as well as the specific quality standards are equivalent to those provided for at EU level. As a result, this mechanism is used and regulated differently in the various member states and the UK (Coppens et al., 2020; see also for a pharmaceutical industry perspective: Hill et al., 2020).

Finally, genome editing techniques uses and dual uses can raise diverse ethic issues that fall mostly under the responsibility of individual EU Member States. Hence, local ethics committees are required to provide an opinion before a clinical trial regarding whether genome editing can be authorised (Isasi, Kleiderman & Knoppers, 2016). Considering the diversity of ethical positions in society and their distribution among EU Member States reported above in section 5.3, it can be expected that the controversies surrounding treatments involving the in vivo use of genome editing treatments in clinical trials and patients will remain highly complex (idem), and difficult to further harmonize without specific legislation.

5.3.4. Research funding

Technology governance can be exercised indirectly through specific rules for access to research funding offered by agencies and programs, both at Member State and EU level. These rules can exclude technologies from funding and create demands of ethical approval and other compliance mechanisms.

The EU and Member States share competencies in the area of research and technological development (Article 4, Treaty on the Functioning of the European Union). The *Treaty on the Functioning of the European Union* (TFEU) establishes that the Union 'shall have the objective of strengthening its scientific and technological bases by achieving a European research area in which researchers, scientific knowledge and technology circulate freely, and encouraging it to become more competitive, including in its industry' (Article 179, TFEU) and lay down a number of activities to pursue towards these objectives, including establishing a multiannual framework program for research and innovation (Articles 179 to 190, TFEU) – currently the research funding program Horizon Europe (Regulation (EU)2021/695 Horizon Europe).

The Horizon Europe Regulation specifically excludes from EU funding research 'activities intended to modify the genetic heritage of human beings which could make such modifications heritable' the only exception being research relating to cancer treatment of the gonads, which can be financed

(Article 18 (1) (b), Regulation (EU)2021/695 Horizon Europe). The structure of the text suggests that the rule is broader than a mere prohibition of germline editing but rather aimed also at any research that could allow to make heritable modifications to the genome, regardless of the type of techniques employed and even if such modifications are unintended. This is extended also to activities carried out outside the EU, since a confirmation is required that the research activities funded would have been allowed in a Member State (Article 19(2)(c), Regulation (EU)2021/695 Horizon Europe).

Compliance with ethical principles and relevant EU national and international law, including the Charter and the European Convention for the Protection of Human Rights and Fundamental Freedoms and its Supplementary Protocols is required (Article 19 (1), Regulation (EU)2021/695 Horizon Europe). The Regulation also imposes an ethics self-assessment identifying and detailing all the foreseeable ethics issues and proposals for funding are to be 'systematically screened to identify actions which raise complex or serious ethics issues and submit them to an ethics assessment' (Article 19(2)(a) and (3), Regulation (EU)2021/695 Horizon Europe).

5.4. National Law: EU Member States and UK

Germline or heritable genome interventions and associate dilemma are more likely to take place in clinical practice in the context of assisted reproduction treatments (ART). Unsurprisingly, most of the existing national legislation applicable, directly or indirectly, to genome editing has been enacted in this context. Genome editing offers hope for parents carrying hereditary diseases linked to specific mutations to have a healthy genetic-related child. In such cases, genetic therapeutic interventions to correct mutations may be considered for legal purposes germline modifications or heritable genome modifications and thus prohibited, despite being therapeutically justifiable in light of medical deontological principles that prioritise individual patient benefit over societal considerations.

In the impossibility to provide for a full review of all national member states, this section provides a few brief examples with the objective to sketch a picture of the diversity present in national legislation in the EU and UK. For convenience of analysis the country examples are presented according to the status towards the Oviedo Convention, which establishes bioethics rules, including the prohibition of heritable human genome editing (Article 13, Oviedo Convention, see section 6.2 above). Its influence in the national legislations in Europe varies in degree. Although countries that have not signed nor ratified the convention, have refused to do so for a variety of reasons, and thus do not necessarily have a legislative framework more liberal towards genome editing.

5.4.1. EU Member States that signed and ratified the Oviedo Convention

i. Denmark

Denmark prohibits the use of genetically modified eggs to establish pregnancies and research involving modification of fertilised eggs beyond 14 days (section 27, Act on Assisted Reproduction). The act also established that assisted reproduction must not take place 'unless the aim is to fuse a genetically unchanged (unmodified) egg cell with a genetically unchanged (unmodified) sperm cell' (section 2, Act on Assisted Reproduction). Basic research involving genetic modification of fertilised eggs up until 14 days after fertilisation is allowed under certain conditions and research and treatment using gene therapy in humans is already being conducted. Research projects must be approved by an ethics committee, and investigational treatments must satisfy additional general rules. The Act on Assisted Reproduction has been subject to revision over the years and according to commentators continues to warrant some criticism (Rothmar-Herrmann, 2018).

ii. France

Bioethics legislation in France is codified under the Public Health Code, which includes norms concerning research on embryos and assisted reproduction (Article L2151-2, Public Health Code). French bioethics legislation is to be updated in light of new technological or scientific developments, and following a national public consultation held at least every five years. The most recent public consultation took place in 2018.

The Public Health Code prohibits the creation of *research embryos*, but it does not provide a definition of embryo (Article L2151-2, Public Health Code). Research on supernumerary embryos and human embryonic stem cells is not expressly prohibited and thus is understood as allowed pursuant to necessary authorisation by the National Biomedicine Agency, a public body created and regulated by the Public Health Code (Article L2151-5, Public Health Code) (Blassimme et al., 2020). Conducting heritable genetic modifications in research aiming at preventing or treating a genetic disease are allowed (Article 16-4, *a contrario*, Civil Code). Clinical applications of genome editing for ART purposes or any activity that could damage the integrity of the human species are strictly prohibited (Article 16-4, Civil Code), and it is also prohibited to transfer to a uterus, with the goal of starting a pregnancy, embryos on which research was carried on (Article L2151-5, Public Health Code). Furthermore, genome editing may also be subsumed to criminal laws against eugenic practices (Articles 214-1, 214-3, 214-4 Penal Code).

iii. Portugal

Portuguese law does not have a specific provision on germline or heritable genome modification, and the law does not refer to genome editing technology. However, the *Act on medically assisted reproduction* (Act 32/2006 of 26 July 2006) limits considerably both clinical uses and research performed on human embryos. Arguably, the use of genome editing techniques with a clear therapeutic purpose in ART could be authorised by the ethical research council. However, the use of ART to improve any non-medical characteristics of the unborn child is punishable severely with up to 2 years of imprisonment or 240 days fine (Article 37, Act on medically assisted reproduction). Likewise, reproductive cloning (Article 36, Act on medically assisted reproduction), and the creation of chimeras and hybrids, results in a prison sentence between 1 to 5 years (Article 38, Act on medically assisted reproduction).

iv. Spain

Two main acts are relevant to genome editing the 2006 Act on Assisted Reproduction Techniques and the 2007 Act on Biomedical Research. Spanish Law prohibits expressly the creation of embryos for experimental purposes (Article 33, Act on Biomedical Research), pursuant to the doctrine of 'gradualist approach towards human life' adopted by the constitutional court (see rulings n. 53/1985, 212/1996 and 116/1999). However, it is permissible the use of any techniques of obtention of embryonic stem cells with both therapeutic goals and research goals as long as it does not include the creation of an embryo (part III - preamble, Act on Biomedical Research).

Research interventions on supernumerary embryos are permitted with less restrictions (Article 34, Act on Biomedical Research and Article 15, Act on Assisted Reproduction Technique). Spanish law permits gamete research, however gametes used in research cannot be transfer into a human uterus, nor used to develop embryos with the goal to establish a pregnancy (Article 14 (2), Act on Assisted Reproduction Techniques).

Therapeutic pre-implantation interventions are allowed provided that the goal is to treat a disease or prevent its transmission. Interventions are subject to requirements of informed consent of the prospective parent(s), and that there the pathologies of the embryo have a clear diagnostic with severe or very severe prognosis and that the treatment offers reasonable possibilities of improvement or cure; that non pathologic hereditary characteristics are modified nor there is goal of racial selection (Article 13, Act on Assisted Reproduction Technique). Interventions on embryos and foetus in the uterus, can only be performed with a diagnostic or therapeutic goal and in the

interest of the embryo/foetus (Article 30, Act on Biomedical Research). Carrying out any intervention aimed at the introduction of a modification in the genome of the descendant is considered to be a serious infraction and as such punishable with a fine of between 10.001 and 1.000.000 euros (Articles 74 (2)(c)(a) and 75(1), Act on Biomedical Research).

Some authors argue that Spanish Law allows germline modification as long as the intervention does not involve the introduction of new genetic material into the human genome, nor have as goal to change the human genome (even if causing it) (de Miguel Beriain & Casabona, 2020).

5.4.2. EU Member States that have signed but not yet ratified the Oviedo Convention

i. Italy

The current legislation - The 2004 Act on Medically Assisted Reproduction - is subject to heated debate and criticism. On different occasions, between 2008 and 2019, some provisions were declared unconstitutional by the Italian Constitutional Court. Italy has also been condemned by the European Court of Human Rights in Case *Costa & Pavan v. Italy* (Application no. 54270/10) concerning access to pre-implantation diagnosis (Fineschi et al., 2005; Penase, 2012; Molinelli et al., 2012, Biodirrito Dossier 2017). A legislative proposal for legislative reform has been presented (Proposal DDL 1630/2014).

The controversial 2004 *Act on Medically Assisted Reproduction* bans any form of eugenic selection of embryos and gametes, or interventions which, by means of selection, manipulation or artificial manipulation, are intended to alter the genetic heritage of the embryo or the gametes or to predetermine their genetic characteristics, with the exception of the interventions for diagnostic and therapeutic purposes (Article 13(3)(b), Act N.40/2004).

The Constitutional Court declared in 2015 this provision partly unconstitutional insofar as it encompasses a prohibition of embryo selection in order to avoid implantation of embryos carrying severe genetic transmissible diseases (Italian Constitutional Court, decision of 18/11/2015).

The interventions on the embryo currently allowed are very narrowly determined. Clinical and experimental research on any human embryo is allowed, but only under two cumulative conditions, that it pursues exclusively therapeutic and diagnostic purposes related to the embryo, aimed at the protection of the health and development of the embryo itself; and provided that alternative methods are not available. (Article 13 (2), Act N.40/2004).

These prohibitions are enforced with penalties between 2 to 6 years of imprisonment and fines between 50.000 to 150.000 euro, and the accessory penalty of suspension from exercising a medical profession between 1 to 3 years (Article 13(4) and (5), Act N.40/2004; See also European Court of Human Rights in Case *Costa & Pavan v. Italy*).

ii. Sweden

Sweden's *Act on Genetic Integrity* (Act on Genetic Integrity SFS n. 2006:351), prohibits the use of treatment methods intended to achieve genetic modifications which can be inherited, and expressly forbids clinical trials with either a research or treatment purpose that involve human genetic modifications capable of being inherited (Ch 2, Paras 3 and 4, Act on Genetic Integrity). Pre-implantation diagnostic is only allowed when parents carry a severe monogenic or chromogenic hereditary disease which has a high risk of resulting in a child with a genetic disease or health damage.

The Act on Genetic Integrity, further expressly forbids embryo selection to choose specific traits, limiting selection to situations where the goal is to avoid implantation of embryos that would result in a child that may inherit a genetic disease or health damage (Ch 4, para 2, Act on Genetic Integrity).

The recently enacted *Act on Aesthetic Surgical Interventions and Aesthetic Injections* (Act 2021:363) could arguably become applicable to somatic genome interventions with a cosmetic purpose. These are defined as interventions with the purpose to modify or preserve appearance of a person (para 2, Act 2021:363) and do not specify composition or mechanism of action beyond being administered by surgery or an injection. The act determines that only licenced medical doctors, nurses and dentists can perform such interventions (para 8, Act n. 2021:363) and prohibits such interventions on minors (para 9, Act SFS n. 2021:363).

5.4.3. European countries that have not signed the Oviedo Convention

i. Belgium

Belgium has one of the most permissible legislations in the European Union concerning genome editing (Boggio et al. (eds), 2021). Belgian applicable laws are the 2005 *Act concerning Research on Embryos In Vitro*, and the 2007 *Act concerning Medically Assisted Reproduction and the Disposition of Supernumerary Embryos and Gametes*.

Belgium bans germline editing for eugenic purposes, i.e., selection or improvement of non-pathological characteristics of the human species, however it allows germline genome editing for elimination or correction of genetic diseases. The statute allows clinical research on the transfer of modified embryos in humans for the purpose of testing gene therapy that benefits the specific embryo is allowed (Act concerning Research on Embryos In Vitro, Article 5), provided that authorisation is obtained from the local ethics committee and the Federal Commission on scientific research on embryos in vitro (Pennings, 2020).

ii. Germany

Germany objected to the Oviedo convention, as it considered its provisions overly permissible clashing with its pre-existing legislation. The Embryo Protection Act (ESchG) defines embryo (paras 8.1 and 8.2, ESchG,) and germline cells (para 8.3, ESchG) although it is disputed whether the definition encompasses artificially created gametes (Faltus, 2020).

The law prohibits basic research on modified gametes adding that these cannot be used for fertilisation (para 5.4, ESchG); the creation of research embryos (para 1.1, ESchG), and any 'use' of embryos for any purpose other than their 'preservation', conversely prohibiting embryo destruction (para 1.1, ESchG; Faltus, 2020).

In theory, genome editing research is allowed as long as it does not result in the destruction of the embryo. However, due to the legal prohibition on modifying human germline cells and, because both clinical research and applications are prohibited, the implant of these embryos is punishable (para 5, ESchG; Faltus, 2020).

The *Embryo Protection Act* contains criminal enforcement provisions, these have also an extra territorial scope of application – allowing to sanction of German-based scientists even when the actions take place abroad, e.g. as part of a research collaboration (para 9(2) Penal Code; Faltus, 2020).

iii. United Kingdom

In the UK any research that alters the germline in embryos requires authorisation from the Human Fertilisation and Embryology Authority (HFEA). The HFEA will typically make approval conditional on the obligation that edited embryos must never be transferred into a human uterus. This entails that clinical use of germline editing is currently banned by UK law, but germline editing research is still allowed. The HFEA first authorisation for genome editing research on human embryos issued in 2016 received great publicity. It was granted to a stem cell researcher studying which genes are crucial for healthy cell division, with the objective of using such knowledge to screen embryos,

potentially preventing miscarriages and aiding fertility. The embryos used were not older than seven days and not intended to be implanted (The Francis Crick Institute, 2016).

The UK was also the first country in the world to allow and regulate mitochondrial replacement therapy, also known as mitochondrial donation (Human Fertilisation and Embryology Act, 2008). The procedure is allowed under UK law but only to avoid severe genetic conditions (Section 35A, c22, Human Fertilisation and Embryology Act). It enables the correction of genetic mutations before these are transmitted from mother to child through transplant of donor genetic material, by replacing the mothers' unhealthy mitochondria with a donor's healthy mitochondria, resulting in a healthy genetic related child inheriting 99.9% of the parents DNA.

In strict legal terms, the technology entails a modification in germ cells transmittable to future generations, by inserting healthy donor genetic material. However, the UK parliamentary and public debates carefully avoided the use of the terminology genome editing, manipulation, modification or similar. Discussions focused mostly on weighting the potential medical risks of using a new assisted reproduction technique against potential benefits of avoiding pain, suffering and loss of life associated with severe diseases.

Arguments used to allow and regulate this procedure are interesting to debates on genome editing since the reasons for allowing mitochondrial replacement therapy can equally apply to therapeutic uses of genome editing technology (Progress Educational Trust, 2015; Cohen et al., 2020).

5.5. Conclusion

The current legal framework governing human genome editing is complex, fragmented and diverse. Some general principles, or at least their interpretation, require revision in light of recent scientific advances. Namely the reliance on categories such as human germline identity or hereditary modifications to the human genome, is problematic and difficult to interpret. The prohibition of eugenics and distinctions between therapeutic and other goals also require additional clarification and specific regulation is often lacking.

Although EU pharmaceutical legislation is comprehensive, experts argue that there is a risk that some genome editing therapeutic products can never be tested in a clinical trial and that non-therapeutic somatic editing uses are left unregulated, which may become problematic in the future.

National legislation of EU member states and the UK shows considerable variety, a situation that is confirmed by recent comparative studies with a broader geographical scope including also non-EU countries (see Slokenberga et al., 2019; Boggio et al. (Eds.), 2020; Baylis et al., 2020).

6. Harmonisation opportunities at EU level

Although there are limitations in the legislative competence of the EU in the area of health, the internal market for health and wellness services and products can and is already subject to considerable EU harmonisation. Provided that there is sufficient consensus, there is ample room to either introduce genome editing-related provisions in existing directives and regulations (vertical approach) or to enact specific genome editing legislation (horizontal approach). Besides legislative intervention, it is also possible to explore alternative or cumulative public and private governance mechanisms.

Harmonised definitions would be beneficial to the internal market of health and wellness services and products. These facilitate legal certainty in the internal market, improving the ability for citizens (as patients and consumers), companies and healthcare providers (public or private) to navigate the different national rules and a fragmented legal landscape. Uniform definitions facilitate comparison and organic approximation of national legislation, policies, and governance structures. Legal

definitions should include appropriate resilience mechanisms to ensure sustained correspondence with scientific knowledge.

Under the current framework for pharmaceutical products, genome editing products are subject to centralised approval procedure. Yet, the current rules on exceptions to the regulatory framework for ATMP's created to grant patient early access – *compassionate use*, *named-patient use* and the *hospital exception* – require further harmonisation. Currently, these mechanisms are interpreted and in practice used differently in the various member states. Thus, there is need to establish further clarification, uniform interpretation, and application of relevant concepts of EU law (for example the concepts of non-routine basis, custom made product and specific quality standards in the hospital exception).

Legal prohibitions based on distinctions between somatic and germline or heritable genome editing are outdated, and unable to serve as legal criteria. Firstly, the distinction is not sufficient for ensuring legal certainty since hereditary modifications can occur where such is not the goal of the procedure; and secondly because when broadly interpreted, germline editing, or heritable editing, defined as interventions making modifications passed onto descendants, can cover and thus prohibit important future therapeutic options to cure genetic diseases.

Genetic eugenics programs prohibited by the EU Charter should be clearly defined and regulated. The prohibitions should apply not only to Member States and public entities, but also to private actors. Eugenics should also be concerned with somatic interventions where these cannot be considered informed and freely consented (e.g. recommended or sponsored by employers; performed on minors; military staff; or institutionalised persons, etc).

Existing restrictions aimed at avoiding eugenic practices should be carefully interpreted or eventually further regulated, clearly exempting at least preventive medicine genome editing, in order to avoid hampering future therapeutic options for individuals and families suffering from severe hereditary diseases and conditions. Likewise, it should be possible to obtain research funding and conduct clinical trials for advanced therapies.

Concerning the use of genome editing in Assisted Reproduction Techniques, the permissibility of these interventions is currently often linked to treating a serious (monogenic) disease. There is an urgent need to define and if possible, harmonize, criteria for determining the seriousness of a given disease, preferably including both medical objective diagnosis criteria and how a given disease will subjectively impact the future child, their family and the community.

The prohibition on eugenic practices needs to be clearly separated from debates and legislative intervention concerning elective or non-strictly therapeutic interventions on consenting adults. Uncontrolled somatic editing can pose great social and ethical risks (e.g. inequality, public health problems, interventions in children and people unable to consent, discrimination, etc.). However, the use of the descriptor *human enhancement* is not useful for an inclusive debate that should rather focus on how to improve standards and practices for informed consent and the legal limits of personal agency concerning genome editing interventions in one's body.

Although a broad review is outside the scope of this report, with few exceptions there is a notable lack of regulations concerning non-surgical cosmetic related interventions on the human body. Where regulated, these are mostly approached under a logic of consumer protection, product safety and civil liability outside public health debates.

There is a need to prevent future public health problems by ensuring that all somatic genome editing is clearly covered by similar rules than those applicable to therapeutical uses by the extensive regulatory framework at EU and national level that regulates medical interventions and medical products, including regulating DIY kits sold via electronic commerce. Issues that require specific attention are among others to determine what type of somatic genome editing

interventions should be banned or restricted; the professional qualifications necessary to perform them; what safety and technical requirements should be in place, etc. Harmonised rules for informed consent including genetic counselling and customer safety in non-medical interventions would also be advisable.

A possible approach would be to define and create specific rules for high-risk genome editing interventions. Possible criteria could include inter alia the following elements: the objectives of the intervention; expected results and whether these can be passed to future generations, are permanent or temporary, and reversible or irreversible; and the respective level of risks the intervention poses for individual and society. The use of a multi-level risk-based approach would allow establishing different obligations on technology developers, providers and users.

The implementation of a risk-based approach should include consideration for not only individual risks and benefits, but also a balance with broader ethical and social considerations. Any such risk-based approach is required to consider the interface with the existing legal and regulatory frameworks used to evaluate medical products and interventions to deal with patient risk benefit where interventions have a therapeutic goal, complemented, if suitable with a precautionary approach more suited to deal with uncertainty and knowledge gaps.

Prohibitions and regulation of interventions in the human body suffer from specific well-known enforcement issues and constitutional limitations. In cases where (hypothetically) genome editing was performed in embryos, minors or other persons unable to consent, a balance is necessary between the needs for prevention and reintegration relating to the specific illicit conduct and the legal rights, interest and wellbeing of the resulting child/person – the victim. Such would be an issue, for example in cases where the penalty includes prison sentences and loss of custody to parents or legal guardians.

Due to the worldwide diversity of national legislations, it is foreseeable that sooner or later the legal status of germline edited persons, embryos and foetuses will need to be considered. Delicate issues involve determining the fate of embryos created and edited in contravention to existing national norms, especially in jurisdictions that do not allow or restrict embryo destruction. Even more complex, but necessary, is regulating the status of edited, implanted but yet unborn, embryos or foetuses, for example whether genome editing performed without parental informed consent is a valid ground for a late term abortion. Finally, if genome edited children are born, any determination concerning long term monitoring requires a careful balance with the rights to respect for privacy, family life, personal integrity and autonomy.

During investigational and evidence gathering activities, considerable enforcement questions may occur concerning data protection, privacy and physical integrity rights of patients and consumers of genome editing. In particular, in situations where victims of the illicit genome editing do not recognise themselves as such and/or refuse being subjected to privacy or body integrity invasive forensic activities. Furthermore, also in this context, the rights of minors and those unable to consent or in situation of vulnerability should be specially safeguarded.

Medical and reproductive travel, as well as beauty and performance improvement tourism, requires increased international collaboration. Restrictions aimed at avoiding high-risk practices should not hamper access to experimental or recently approved therapeutic options for individuals and families suffering from severe hereditary diseases and conditions, including the possibility to seek medical attention in other countries or to participate in clinical trials legal under the said jurisdiction.

Conversely, the private importation of counterfeited and falsified products (dangerous or inefficient) from outside the EU that do not conform with safety and certification rules is a known phenomenon with dire implications for both public health and a commercial IPR perspective. Ongoing or future interventions to tackle this issue should take genome editing into consideration,

since it is likely that genome editing services and products, real or falsified, will sooner or later also be advertised and sold through unscrupulous digital channels.

Private governance through technology-licensing agreements and other contractual means (e.g. terms and conditions of use, company by-laws, voluntary codes of conduct, etc.) already plays a large role in the governance of emerging technologies. While ethical license pledges are a positive sign from the industry, there is very little agreement in their normative content (similarly, there is also considerable discussion on what constitutes a FRAND licence - fair, reasonable, and non-discriminatory in the context of standard essential patents). Development of general guidance or model clauses for standard ethical licensing in genome editing and other biomedical innovation could provide a clear signal to stakeholders and promote good private governance, while preserving contractual freedom.

Genetic testing, and the use of genetic big data analytics and AI systems both in health care and other commercial settings is experiencing continuous development. The possibility to use of big data-based AI systems to identify favourable traits or perceived favourable traits, matching with a possible non-therapeutic genome editing intervention may become a future area of concern. Regardless of the type of approach to regulation chosen this is a related area that also would benefit from a coordinated regulatory intervention.

7. Governance principles and tools

The analysis of ethical and legal recommendations, principles and frameworks proposed to address the governance of human genome editing revealed a plurality of perspectives, approaches, and concerns. The following have emerged as most cited and/or to some degree generally agreed upon:

1. The respect for the principle of legality (rule or law) and human rights needs to be carefully embedded in all forms of governance.
2. Safety concerns and pathways for clinical translation, including the formulation of standards, are to be addressed from an integrated cross-disciplinary perspective and not in a merely technical-formalistic manner.
3. There is a need to establish permanent (public and private) governance structures and institutional bodies dedicated to genome editing (at international, EU and/or national level), including genome editing registries.
4. International and EU Member State cooperation and coordination is essential.
5. There is a strong need for an inclusive, fair and transversal social debate with multi-level stakeholders, including meaningful participation opportunities for healthcare professionals and patient groups representing those more likely to be impacted by regulation and to benefit from the technology.
6. Private governance mechanisms play an important role and should be encouraged and complemented with public governance mechanisms (such as laws and regulations) to foster: (a) openness, transparency, trustworthiness and accountability; (b) fair and responsible stewardship; (c) accessibility, availability, acceptability and quality of healthcare and health-related services and products.
7. All forms of governance (public or private) should be carefully guided and informed by ethics principles and established state-of-the-art scientific findings, as well as include dynamic mechanisms to ensure resilience to technical advances and evolving society and technology-related phenomena.

8. While common principles are necessary and should be developed, it is of paramount importance that ethical and legal pluralism between different communities, regions and countries remains to be respected, but only insofar as the respect for human rights and fundamental principles of EU law is ensured.
9. While research, clinical trials, clinical practice and non-medical commercial activities or off-label uses require specific and diversified regulatory mechanisms, these should also ensure a minimum level of coherence and consistency of normative content.
10. Any governance mechanisms should consider that regulating interventions on the human body requires respect for collective and individual human dignity and human autonomy/agency, improving available mechanisms and practices for patients or users to exercise their right to informed consent, participate in healthcare decisions and benefit from scientific advances. Long-term monitoring of genome-edited patients or inclusion in genome-editing public registries should be carefully balanced with the necessary respect for privacy, family life and data protection.

8. Conclusions

The present report provides a critical contextual legal analysis and comparison of different legislative and regulatory approaches to human genome editing, as well as options for general governance principles and frameworks.

The reviewed literature contains a rich variety of academic discussions, perspectives and opinions on the ethical, legal and social implications of genome editing. These concentrated on human germline or hereditary genome editing. A large amount of attention was dedicated to discussing how and to what degree to enact and enforce prohibitions of eugenics, in particular in the contexts of assisted reproductive technologies and human enhancement.

Opinions vary from libertarian and techno-optimistic views on human genome editing as a vector for promoting the wellbeing and moral and physical improvement of humanity, to bio-conservative, human-nature-inviolability ontological considerations and precautionary approaches to this technology. Between these extremes on the opinion spectrum, a broad range of opinions and concerns are directed by specific needs and challenges.

It is widely agreed that the regulation of emerging technologies requires an inclusive, multi-disciplinary and transversal debate. In this sense, the present report reviewed proposed frameworks and recommendations for governance and ethical guidance reports. These were issued by different international bodies and organisations, national ethics councils and the European Group of Ethics.

This analysis revealed a large consensus on the idea that further regulation and governance mechanisms and frameworks are necessary. Secondly, the ethics and scientific communities, represented by a broad range of disciplines, are determined to participate in the development of such discussions. The analysis of ethical, legal and social implications of human genome editing has until recently been organised in two major groups, depending on whether the intervention is restricted to a patient/user or also affects their descendants.

Somatic human genome interventions are approached mostly from a perspective of medical and health law and the regulatory approval of medical and pharmaceutical products for human use, while interventions on the human germline are considered from ontological viewpoints, as these are considered to pose global and broader risks to human nature, human civilisation and societies.

This traditional divide was recently bridged in most review reports and statements. It is now generally recognised that the risks and benefits of each intervention require a deeper consideration, depending on a complex number of factors (e.g. medical, ethical, and social) that cannot simply be reduced to whether an intervention involves hereditary modifications or not.

The overview analysis of the existing international, European and EU frameworks and legislation applicable to human genome editing revealed an extensive but fragmented regulatory framework. A legal comparison of rule and normative approaches to genome editing in selected EU Member States and the United Kingdom demonstrates that, while a strong legal and regulatory framework applicable to genome editing already exists, there are ample opportunities for further development in certain areas of EU harmonisation, through legislative initiatives, policy guidance or incentives to private governance.

Part III: Policy options

This section presents a number of policy options in the form of a table. It contains a synthesis of commonly found principles and associated actions, based on the review of the technology conducted in Part I and the conclusions of the analysis contained in Part II of the present report. It considers numerous sources, which were reviewed and analysed. These sources include scientific and academic studies, recommendations, reports and policy papers by several international institutions and interest groups.

<i>Policy options</i>	
<i>Principles of governance</i>	<p>Rule of law, human rights and democratic values</p> <p>All forms and initiatives concerning governance (public or private) and at all levels (national, EU, international) should ensure respect for the principle of legality (rule or law), human rights and democratic values.</p>
	<p>Human dignity, autonomy and agency</p> <p>Regulation of interventions on the human body requires the improvement of the mechanisms and practices available for patients or users to exercise their rights to informed consent, to participate in healthcare decisions and to benefit from scientific advances. Long-term monitoring of genome-edited patients or inclusion in genome-editing public registries should ensure respect for privacy, family life and data protection.</p>
	<p>Inclusive debate(s)</p> <p>Governance of genome editing should provide forums for inclusive, fair and transversal social debate(s) with multi-level stakeholders. In particular, opportunities for meaningful participation should be afforded to individuals and groups representing those more likely to be impacted by technology and its regulation – researchers, healthcare professionals, patients and their families.</p>
	<p>Public health and individual safety</p> <p>Inter-, cross- and trans-disciplinary perspectives and approaches should be integrated in the evaluation of safety concerns and pathways for clinical translation. Including ethical and social science considerations.</p>
	<p>Interface between public and private forms of governance</p> <p>Private mechanisms of technology governance play an important role and should be encouraged to foster:</p> <ul style="list-style-type: none"> (a) openness, transparency, trustworthiness and accountability; (b) fair and responsible stewardship; (c) accessibility, availability, acceptability and quality of healthcare and health-related services and products.
	<p>Ethical and legal pluralism</p> <p>Development of common principles should ensure respect for ethical and legal pluralism between different communities, regions and countries, insofar as the respect for human rights and fundamental principles of EU law is preserved.</p>
	<p>Coherence and consistency of normative content</p> <p>All regulatory interventions should ensure a minimum level of coherence and consistency of normative content capable of creating legal certainty and facilitating compliance, regardless of the need to use diversified regulatory mechanisms and approaches to specific sectorial regulation.</p>

	<p>Dynamic and resilient regulation</p> <p>Governance interventions should include dynamic mechanisms to ensure resilience to the continuous technical advances and evolving social-technology-related phenomena, by ensuring that governance initiatives are guided by ethics principles and informed by the scientific state-of-the-art.</p> <p>Dedicated governance structures</p> <p>Public and private governance structures and institutional bodies dedicated to genome editing (at international, EU and/or national level) should be established, supported or developed, including genome editing registries.</p> <p>Transnational cooperation</p> <p>International and EU Member State cooperation and coordination of regulatory efforts and related enforcement should remain a priority.</p>
<i>Mechanisms of regulation and action</i>	<p>European Union</p> <ul style="list-style-type: none"> – Harmonisation of legislation at EU level. – Mechanisms of coordination and oversight via EU institutions (European Medicines Agency – EMEA). – Revision of the Biotechnology Directive or updated guidelines for interpretation and patent examination; – Revision of regulations to remove barriers to research and clinical trials for all therapeutic applications pursuant to careful benefit-risk assessment. <p>National level</p> <ul style="list-style-type: none"> – Updating national legislation to face the challenges posed by genome editing. – Ensuring the existence of national mechanisms for uncovering breaches of regulations or absence of regulations and study concerns with the national regulatory authority. <p>EU international role</p> <ul style="list-style-type: none"> – Assuming a leadership role in promoting and developing regulatory efforts and mechanisms. – EU participation in and support for international initiatives concerning the creation of an international scientific advisory panel of multidisciplinary, independent experts to assess scientific efficiency and safety. – EU participation in and support for an international body to make recommendations on accepted uses and limitations.

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Annex

Table 1 – Recommendations made by the National Academy of Medicine, National Academy of Sciences, and the Royal Society (adapted from Box S-1, National Academies, 2020)

Recommendation 1: No attempt to establish a pregnancy with a human embryo that has undergone genome editing should proceed unless and until it has been clearly established that it is possible to efficiently and reliably make precise genomic changes without undesired changes.

Recommendation 2: Extensive societal dialogue should be undertaken before a country makes a decision on whether to permit clinical use of heritable human genome editing (HHGE).

Recommendation 3: Clinical use of HHGE should proceed incrementally. It is not possible to define a responsible translational pathway applicable across all possible uses.

Recommendation 4: Initial uses of HHGE, should be limited to circumstances that cumulatively meet the following criteria:

- serious monogenic diseases causing severe morbidity or premature death;
- changing only a pathogenic genetic variant known to be responsible for the serious monogenic disease to a sequence that is common in the relevant population and that is known not to be disease-causing;
- embryos without the disease-causing genotype will not be edited and transferred;
- prospective parents must have attempted at least one cycle of preimplantation genetic testing without success (i) have no option for having a genetically-related child without the serious monogenic disease, or (ii) have extremely poor options (expected proportion of unaffected embryos 25% or lower).

Recommendation 5: Preclinical evidence based on a significant cohort of edited human embryos, should a priori demonstrate that the process has the ability to generate and select, with high accuracy, suitable numbers of embryos that:

- have the intended edit(s) and no other modification at the target(s);
- lack additional variants introduced by the editing process at off-target sites;
- lack evidence of mosaicism introduced by the editing process; are of suitable clinical grade to establish a pregnancy, and have aneuploidy rates no higher than expected based on standard ART procedures.

Recommendation 6: A proposal for clinical use should also include plans to evaluate human embryos prior to transfer using:

- developmental milestones until the blastocyst stage comparable with standard in vitro fertilisation practices, and
- a biopsy at the blastocyst stage that demonstrates:
 - the existence of the intended edit in all biopsied cells and no evidence of unintended edits at the target locus, and
 - no evidence of additional variants introduced by the editing process at off-target sites.

It is vital to monitor a resulting pregnancy and long-term follow-up of resulting children and adults.

Recommendation 7: Research should continue also into the development of methods to produce functional human gametes from cultured stem cells.

Recommendation 8: Countries considering clinical HHGE should have mechanisms and competent regulatory bodies to ensure the following cumulative conditions:

- individuals conducting HHGE-related activities, and their oversight bodies, adhere to established principles of human rights, bioethics, and global governance;
- the clinical pathway for HHGE incorporates best practices from related technologies such as mitochondrial replacement techniques, preimplantation genetic testing, and somatic genome editing;

- decision making is informed by findings from independent international assessments of progress in scientific research and the safety and efficacy of HHGE, which indicate that the technologies are advanced to a point that they could be considered for clinical use;
- prospective review of the science and ethics of any application to use HHGE is diligently performed by an appropriate body or process, with decisions made on a case-by-case basis;
- notice of proposed applications of HHGE being considered is provided by an appropriate body;
- details of approved applications are made publicly accessible, while protecting individual privacy (including genetic condition, procedures, performing laboratory or clinic, and oversight authority);
- publishing in peer-reviewed journals of detailed procedures and outcomes;
- enforcement of norms of responsible scientific conduct;
- researchers and clinicians organise and participate in open international discussions on the coordination and sharing of results of relevant scientific, clinical, ethical, and societal developments impacting the assessment of HHGE's safety, efficacy, long-term monitoring, and societal acceptability;
- prior development of practice guidelines, standards, and policies for clinical uses of HHGE,
- deviation from established guidelines is reported, received and reviewed, and sanctions are imposed where appropriate.

Recommendation 9: An International Scientific Advisory Panel (ISAP) should be established. The ISAP should have a diverse, multidisciplinary membership and should include independent experts who can assess scientific evidence of safety and efficacy of both genome editing and associated assisted reproductive technologies. The ISAP should:

- provide regular updates on advances in, and the evaluation of, the technologies that HHGE would depend on and recommend further research developments that would be required to reach technical or translational milestones;
- assess whether preclinical requirements have been met for any circumstances in which HHGE may be considered for clinical use;
- review data on clinical outcomes from any regulated uses of HHGE and advise on the scientific and clinical risks and potential benefits of possible further applications;
- provide input and advice on any responsible translational pathway to the international body described in Recommendation 10, as well as at the request of national regulators.

Recommendation 10: In order to proceed with applications of HHG that go beyond the translational pathway defined for initial classes of use, an international body with appropriate standing and diverse expertise and experience should evaluate and make recommendations concerning any proposed new class of use. This international body should:

- clearly define each proposed new class of use and its limitations;
- enable and convene ongoing transparent discussions on societal issues surrounding the new class of use;
- make recommendations concerning whether it could be appropriate to cross the threshold of permitting the new class of use;
- provide a responsible translational pathway for the new class of use.

Recommendation 11: An international mechanism should be established to monitor research or conduct of heritable human genome editing deviating from established guidelines or recommended standards

Table 2 – Recommendations of the WHO Expert Advisory Committee on Developing Global Standards for Governance and Oversight of Human Genome Editing (adapted from WHO, 2021)

1. Leadership by WHO and its Director-General

The WHO and its Director-General should demonstrate both scientific and moral leadership, by:

- (i) being open about the opportunities and challenges inherent to human genome editing (HGE);
- (ii) clearly stating the ethical aspects of HGE, and
- (iii) outlining the consequences of failing to address the ethical issues.

2. International collaboration for effective governance and oversight

The WHO should collaborate to develop and implement a shared vision for an ongoing international process to:

- (i) identify and develop points of agreement or convergence;
- (ii) establish a process for identifying key decision points;
- (iii) explore opportunities for collaborative engagement, standard-setting, investigation and oversight, and
- (iv) share information on relevant existing and planned policies (laws, regulations and guidelines).

In the interim, the Director-General should institute a cross-institutional approach, including to:

- (i) task the regulatory strengthening and capacity building teams within WHO's Department of Essential Medicines and Health Products to begin working on integrating HGE into their activities;
- (ii) convene a meeting of regulators from MS on the feasibility of international agreements, capacity building needs and possibilities for harmonisation, and
- (iii) task the Science Division to convene meetings on HGE in each of the six WHO regional offices with regulators and relevant bodies (medical and scientific leaders, patient groups, civil society organisations, etc.).

3. Human genome editing registries

The WHO should:

- (i) ensure that clinical trials using somatic HGE technologies are reviewed and approved by the appropriate research ethics committee before inclusion in the Registry of HGE clinical trials;
- (ii) request that clinical trials registries make use of keywords to identify those using HGE technologies;
- (iii) develop a mechanism to identify clinical trials using HGE technologies that may be of concern;
- (iv) establish a small expert committee to regularly monitor the clinical trials Registry and to develop and review a set of international standards for clinical trials involving HGE for the clinical trials registry, and
- (v) support the scientific community to develop an additional basic and preclinical research registry.

4. International research and medical travel

The Director-General, in consultation with the Science Council, should make a policy statement that somatic or germline HGE research should only take place in jurisdictions with domestic policy and oversight mechanisms.

The WHO, with guidance from the Science Council, should integrate into all of its relevant activities a focus on fostering responsible international research and medical travel.

5. Illegal, unregistered, unethical or unsafe research and other activities

The WHO, with advice from its Science Council, should charge the Science Division to lead an effort to create a multisector collaboration to develop an accessible mechanism for confidential reporting of concerns about possibly illegal, unregistered, unethical and unsafe HGE research and other activities.

6. Intellectual property

The WHO should:

- (i) work with others to encourage relevant patent holders to ensure equitable access to HGE interventions;
- (ii) encourage industry to work with resource constrained countries to build capacity to take advantage of HGE inventions, and
- (iii) convene a meeting of those holding or applying for patents relevant to HGE, industry bodies, international organisations, such as the WIPO and the WTO, and those involved in establishing or running relevant patent pools to explore the potential for the adoption of appropriate ethical licensing requirements.

7. Education, engagement, and empowerment

The Director-General should:

- (i) call upon the UN Secretary-General to establish a UN interagency working group on frontier technologies that facilitates global dialogue and produces a report outlining the implications of innovative technologies, including HGE, and the ethical frameworks to guide their application, and

- (ii) call for an inclusive dialogue on the future of HGE, including scientific, ethical and societal aspects.

The WHO should:

- (i) develop models of best practice of inclusive multidirectional, multistakeholder dialogue, and supporting materials, that can be applied to HGE, and
- (ii) explore how best to include in decision-making under-represented groups.

8. Ethical values and principles for use by the WHO

The WHO should charge the health ethics and governance unit in the Science Division to lead an effort to create a set of officially endorsed and clearly defined ethical values and principles for use by its expert committees and in WHO deliberations. These values and principles should be built on public health goals and priorities. These should go beyond the WHO workforce and provide an important road map for progress towards the Organisation's goals.

9. Review of the recommendations

In no more than 3 years, WHO's Science Division should initiate an extensive review of these recommendations and the progress made to implement them. This review should not take longer than 18 months and should take into account scientific, technological, and societal changes, adequacy of implementation and assessment of impact, and potential future needs or concerns.

Table 3 – WHO Governance Framework (adapted from Table 3 WHO, 2021)

Ethical values and principles	Commitments associated with these ethical values and principles
1. To inform how decisions are made:	
Openness, transparency, honesty and accountability	<p>A commitment to openness that invites collaborative ambition and work, as well as a commitment to use transparent, honest and accountable processes in order to generate and share evidence-informed, accessible and timely information about:</p> <ul style="list-style-type: none"> (i) best available data (including information about sources of funding, access and outcomes); (ii) guiding ethical values and principles; (iii) actionable policy options for HGE.
Responsible regulatory stewardship.	<p>A commitment to support and promote legitimate, evidence-informed:</p> <ul style="list-style-type: none"> (i) law and regulation; (ii) programme management and measurement; (iii) data collection, storage, processing, distribution and destruction in accordance with privacy rules; (iv) research training and capacity-building, and (v) public awareness about the potential benefits, harms and limitations of HGE in ways that balance competing influences and demands.
Responsible stewardship of science	<p>A commitment to:</p> <ul style="list-style-type: none"> (i) pursue rigorous, evidence-informed basic and applied research with appropriate caution for uncertainty and risk; (ii) follow established ethical practices for research involving humans with particular attention to issues of integrity and conflict of interest; (iii) maximise the potential benefits while minimising the potential harms, and (iv) respect research ethics guidelines and applicable legislation. <p>More particularly, a commitment to align the processes and outcomes of HGE with the values, needs and expectations of society, as identified through participatory approaches involving various publics.</p>
Responsible stewardship of research resources	<p>A commitment to use responsibly finite research resources (biological materials; research skills, and research funding). This requires careful attention to scientific value and validity, as well as social value and validity.</p>
2. To inform what decisions are made	
Inclusiveness	<p>A commitment to carefully consider knowledge and perspectives on HGE informed by different social, cultural and religious beliefs and moral values, as well as different skill sets. In addition, a commitment to ensure that HGE research (basic and applied) and clinical care are representative of global human diversity and are globally accessible.</p>
Caution	<p>A commitment to exercise appropriate caution given existing uncertainty and risk.</p>
Fairness	<p>A commitment to fair dealings with individuals, organisations, nations and publics, in support of collective well-being and the common good. A special commitment to benefit sharing to participants and communities whose samples and data are used for research (e.g. co-research opportunities, sharing of skills and research capacity and priority access to the benefits of research).</p>
Social justice	<p>A commitment to develop HGE in ways that:</p> <ul style="list-style-type: none"> (i) promote human health, collective well-being and the common good; (ii) look after the needs of communities experiencing greater health burdens; (iii) reduce socioeconomic inequality, and (iv) avoid discrimination.
Non-discrimination	<p>A commitment to celebrate and promote diversity by rejecting concepts of eugenics and</p>

	discrimination based on personal or group characteristics (e.g. race, ethnicity, colour, religion, sex, gender, sexual orientation, age, and mental or physical ability).
Equal moral worth	A commitment to recognise and treat all people as having equal moral worth and their interests as deserving of equal moral consideration, with a particular need to recognise and protect the interests of persons with disabilities and of future generations.
Respect for persons	A commitment to respect the wishes of competent individuals regarding the most intimate aspects of their lives, including their health and their reproductive options. In addition, a commitment to promote the best interests of individuals who are not competent to make decisions for themselves.
Solidarity	A commitment to live and work in harmony, grounded in the recognition of the interdependence of humans. In addition, a commitment to share the benefits and burdens of research and clinical care among all people, to minimise the risk of exploitation and to promote the common good.
Global health justice	A commitment to equitable access to opportunities and potentially beneficial outcomes from HGE for all people, particularly those living in low- and middle-income countries. This includes equitable access to support for health research and for the development of health interventions that are appropriate and affordable for the widest possible range of populations with a view to reducing socioeconomic inequality. It also includes equitable protection from potential coercion, exploitation and other harms

Genome editing is a powerful new tool allowing precise additions, deletions and substitutions in the genome. The development of new approaches has made editing of the genome much more precise, efficient, flexible, and less expensive, relative to previous strategies.

As with other medical advances, each such application comes with its own set of benefits, risks, ethical issues and societal implications, which may require new regulatory frameworks. Important questions raised with respect to genome editing include how to balance potential benefits against the risk of unintended harms; how to govern the use of these technologies, and how to incorporate societal values into salient clinical and policy considerations.

This STOA study provides an overview of human genome editing applications and a review of the principles that guide the governance of genome editing in humans, at EU level and worldwide. The study also formulates a series of policy options targeted at basic research and to clinical applications, both somatic and germline.

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