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Governance of Heritable Human Genome Editing – Developing a Regulatory Framework for a Transformative Technology

Natacha Tang*

Abstract: With the discovery of CRISPR and its potential uses in genome editing of the human germline, the end to hereditary diseases and infertility seems closer than ever before. However, as is always the case with emerging transformative technologies, there are caveats. This paper seeks to explore possibilities and pitfalls in the regulation of and policy-making around heritable human genome editing, with a focus on the international (bioethics) law and human rights law perspective.

Keywords: Genome Editing, international law, human rights law, bioethics, policymaking, responsible research

La gouvernance de l'édition du génome humain héréditaire : élaboration d'un cadre réglementaire pour une technologie transformatrice

Résumé : Avec la découverte de CRISPR et de ses utilisations potentielles dans l'édition de la lignée germinale humaine, la fin des maladies héréditaires et de l'infertilité semble plus proche que jamais. Cependant, comme toujours au cas des nouvelles technologies transformatrices, il y a des mises en garde. Cet article cherche à explorer les possibilités et les difficultés de la gouvernance et l'élaboration de politiques autour de l'édition du génome humain héréditaire, en mettant l'accent sur la perspective du droit international (bioéthique) et des droits de l'homme.

Mots-clès : Édition du génome, droit international, droits de l'homme, bioéthique, élaboration de politiques, recherche responsable

Regulierung des Genome Editing am menschlichen Erbgut – Entwicklung eines Rechtsrahmens für eine transformative Technologie

Zusammenfassung: Mit der Entdeckung von CRISPR und seinen potenziellen Einsatzmöglichkeiten der Geneditierung an der menschlichen Keimbahn scheint das Ende von Erbkrankheiten und Unfruchtbarkeit näher denn je. Doch, wie immer bei aufkommenden transformativen Technologien, gibt es auch hier Vorbehalte. In diesem Beitrag sollen die Möglichkeiten und Schwierigkeiten bei der Regulierung und der politischen Entscheidungsfindung im Zusammenhang mit vererbbaren Eingriffen in die menschliche Keimbahn untersucht werden, wobei der Schwerpunkt auf dem internationalen (Bioethik-)Recht und den Menschenrechten liegt.

Keywords: Genome Editing, internationales Recht, Menschenrechte, Bioethik, Politikgestaltung, verantwortungsbewusste Forschung

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1 Introduction

For millennia, humans have been engineering plant and animal life through selective breeding (Smolenski 2015; Ethics Council of the Max Planck Society 2019). With the discovery of deoxyribonucleic acid (DNA) in the 1950s (Yotova 2020), the subsequent rise of molecular biology, and the development of recombinant DNA technologies, scientists were soon able to deliberately alter the genetic makeup of living beings.[1] The recent discovery of the groundbreaking clustered regularly interspaced short palindromic repeats (CRISPR) technology has without a doubt revolutionized the world of genome engineering – never has there been a more precise, efficient, rapid, and cost-effective instrument to edit DNA (Rubeis 2018; NAS 2020; Niemiec and Howard 2020). The benefits are evident: Advancements in the medical field could be greatly accelerated with this novel technology (Tomlinson 2018). Extensive research involving human embryos may offer monumental insight into the human body (Yotova 2020). In particular, the therapeutic use of CRISPR could aid in alleviating hereditary diseases and disabilities as well as infertility (Araújo 2018; Cavaliere 2018; Drabiak 2018; Rubeis 2018). Nevertheless, its application has been heavily debated from the outset (Coller 2019; Baylis et al. 2020), its use to edit the human germline (i. e., heritable) DNA being especially controversial given the potential implications of such ventures (Li and Yin 2020), notably safety and efficacy concerns, ethical and legal issues revolving around autonomy and informed consent, and with that instrumentalization and commodification of embryos and children, the blurred line between the concepts of therapy in contrast with enhancement and even "new eugenics", as well as worries about the impact on social justice (Coller 2019; Baylis et al. 2020).

The human genome "underlies fundamental unity of all members of the human family, as well as the recognition of their inherent dignity and diversity" (see art. 1 of the Universal Declaration on the Human Genome and Human Rights [UDHGHR]), and many consider it to constitute the integrity of humanity as a species (von Hammerstein et al. 2019). Thus, substantial deliberation on heritable genome editing is certainly warranted, since arbitrary application of the CRISPR technology may threaten the integrity of the human genetic inheritance and therefore the human identity and human dignity (NCB 2018; Tomlinson 2018, 450, speaking of "dual-use technology", which "can be used for either ethical or malign purposes"). All the same, it looks like this disruptive technology (Graves and Cook-Deegan 2019; Martin et al. 2021; see Nickel 2020 on disruptive innovation in general and Taeihagh et al. 2021 on what regulatory challenges they pose) and heritable human genome editing is here to stay – one needs only point to the experiment conducted by Chinese scientist Jiankui He (Greely 2019), who has edited the DNA of twin girls subsequently brought to term in 2018, to recognize

1 E. g., by way of DNA combination, with which transgenic organisms are created (NCB 2016).

the urgent need for global regulation of human germline genome editing, even if such a procedure is a long way from being approved by the scientific community (Baylis et al. 2020; Yotova 2020).With that in mind, this paper seeks to provide an overview of the current legal landscape governing human germline genome editing and from there, taking into consideration the suggestions of various authors and institutions, aims at discussing the possibilities and caveats in the process of regulating this powerful technology internationally. To conclude, it will offer suggestions for a consolidated approach.

2 The Current Standing

While the modification of a person's non-heritable (i.e., somatic) DNA is deemed admissible and is safeguarded by cohesive ethical and regulatory frameworks, this is not the case for modifications of heritable human DNA (i.e., the germline) (Rodriguez 2016; Coller 2019; Gyngell et al. 2019; Yotova 2020).[2] Nevertheless, there are hard and soft law provisions governing human germline genome editing to a certain extent (Garden and Winickoff 2018). Assessing that extent will help guide the conversation about how heritable human genome editing may be regulated in the future.

2.1 National Laws

Even though the detailed discussion of domestic regulations of human germline genome editing exceeds the scope of this paper, it is worth noting that across the globe, laws and policies governing gene editing vary widely depending on the underlying legal traditions and social or cultural contexts. Many countries have prohibited heritable genome editing by employing a range of regulatory tools of different intensity (Araki and Ishii 2014; Charo 2016; Baylis et al. 2020; Liu 2020; NAS 2020). In Switzerland, for instance, editing the human germline is outlawed by art. 119 para. 2 of the Swiss Constitution as well as art. 35 of the Swiss Reproductive Medicine Act (Sprecher 2020). The U.S., remarkably, did not explicitly ban such practices (Charo 2016; Johnston 2020), but has instead imposed a moratorium overseen by the Federal Drug Administration and the National Institutes of Health (Araki and Ishii 2014; Drabiak 2018; Liu 2020; NAS 2020). A large number of countries remain ambiguous as to their position concerning this matter (Araki and Ishii 2014; Baylis et al. 2020; Liu 2020).

2 A question to consider is whether this distinction is still possible (see Evans 2021, 1–7, on "the fall of the somatic/germline barrier").

2.2 International Law

While there are hardly any legally binding instruments of international law regulating germline genome editing specifically, several treaties (legally binding) and soft-law instruments (not legally binding) cover the larger scope of international bioethics law and international human rights law, both of which are significant in the field of genomic technology (Boggio et al. 2020; Yotova 2020), as they shed light on the already established international consensus on genetic engineering (Yotova 2020).

2.2.1 Hard Law

2.2.1.1 Oviedo Convention

The Oviedo Convention, its objective being the preservation of human dignity, rights and freedoms, and human welfare (art. 1 and 2 Oviedo Convetion; Charo 2016; Krekora-Zajac 2020), is currently the sole legally binding instrument of international law expressly prohibiting heritable genome editing (art. 13 Oviedo Convetion). However, only a number of member states of the Council of Europe, e. g. Switzerland, have ratified it[3] (Boggio et al. 2019), such that its jurisdictional reach is limited (Isasi and Knoppers 2015), even though, as a "framework treaty" (Boggio et al. 2020, 160), it is designed to be an articulation of basic consensus and minimum standards in bioethics (Deuring 2020). Based on these principles, additional protocols may be adopted to substantiate the rules in a particular scientific field (Deuring 2020).

Art. 13 of the Oviedo Convention allows for therapeutic and preventative use of genome editing technologies inducing non-heritable modifications only, while on the other hand, genetic interventions aiming at modifying the DNA of descendants are explicitly forbidden. The Oviedo Convention establishes the principle of primacy of the human being, i. e., that the interests of the individual prevail over public interests in the field of biomedicine (art. 2 Oviedo Convention). Furthermore, the treaty contains provisions on medical research especially concerning research subjects incapable of giving consent (art. 5–9 Oviedo Convention) and prohibits the conception of human embryos for research purposes, all while calling for adequate protection of embryos where in-vitro research is permitted (art. 18 Oviedo Convention), though without specifying the conditions.[4] Art. 17 of the Oviedo Convention codifies the proportionality requirement.[5]

3 The list of signatories is available at https://www.coe.int/en/web/conventions/full-list?module=signatures-by-treaty&treatynum=164 (accessed December 11, 2022).

4 It is worth noting that the Oviedo Convention does not declare embryos as subjects of human rights, instead broadening its scope of protection by defining the term "human" broadly to encompass all that belong to the human species (see Deuring 2020; Yotova 2020).

5 This, by extension, calls for adequate risk assessment and management (Yotova 2020).

2.2.1.2 Cartagena Protocol and Nagoya Protocol

While not governing human genome editing in particular, the Cartagena Protocol[6] and the Nagoya Protocol[7], both supplements to the widely accepted Convention on Biological Diversity[8], deal with the "safe handling, transport and use" of genetically modified organisms to ensure environmental safety as well as human health (art. 1 Cartagena Protocol) and contain "further compliance provisions in an effort to even the genetic engineering playing field" (Tomlinson 2018, 466). The Cartagena Protocol puts an emphasis on the precautionary principle (preamble, art. 1, art. 10 para. 6, and art. 11 para. 8 Cartagena Protocol), while the Nagoya Protocol sets out to take measures in relation to access to genetic resources, benefit sharing and compliance.[9] Notably, there is a reporting system in place for activities related to genetically modified organisms that may have negative effects on biodiversity or human health (Tomlinson 2018; art. 8 Cartagena Protocol).

2.2.2 Soft Law (International Bioethics Law)[10]

Heritable human genome editing is not only governed by international hard law, but by soft law instruments alike. These instruments include stipulations issued by non-governmental institutions such as universities, foundations or companies (Ikenberry 2004), as well as intergovernmental bodies (i. e., international organizations like the United Nations Educational, Scientific and Cultural Organization [UNESCO]) and non-binding declarations issued by states (Boggio et al. 2020).

The most salient soft law instruments in the field of bioethics are the 1997 UNESCO Universal Declaration on the Human Genome and Human Rights (UDHGHR), the 2003 UNESCO International Declaration on Human Genetic Data (IDHGD), the 2005 UNESCO Universal Declaration on Bioethics and Human Rights (UDBHR) and the 1997 UNESCO Declaration on the Responsibilities Towards Future Generations (DRTFG). Furthermore, several non-governmental institutions have issued recommendations with regards to how heritable human genome editing should be regulated; they shall be discussed in more detail below, as they have been promulgated tailored to heritable human genome editing in particular.

2.2.2.1 UNESCO Universal Declaration on the Human Genome and Human Rights

The UDHGHR is arguably the most important international soft law instrument of "human genome governance" (Kuppuswamy 2009; Boggio et al. 2020, 31 and 34), setting out widely accepted standards and good practices for genome engineering (Yotova 2020). The declaration aims at protecting the identity and integrity of

6 Ratified by 173 parties; see https://bch.cbd.int/protocol/parties/ (accessed April 15, 2022).
7 With 136 ratifications; see https://www.cbd.int/abs/nagoya-protocol/signatories/ (accessed April 15, 2022).
8 196 parties; see https://www.cbd.int/information/parties.shtml (accessed April 30, 2022).
9 See https://www.cbd.int/abs/about/ (accessed April 30, 2022).
10 The term "international bioethics law" as used in this paper shall be understood to encompass all soft law instruments governing the field bioethics.

future generations by shielding the human genome from undue manipulation (Andorno 2013; Boggio et al. 2020).

One of its core principles, the concept of a common heritage of humanity expressed in art. 1 UDHGHR, highlights the global responsibility in the field of genomics (UNESCO IBC 2015; Deuring 2020). It has multiple dimensions: Non-appropriation, international management, benefit sharing, peaceful use, and preservation for the benefit of future generations (Baslar 1998).[11] The human genome is deemed common "property" and thus needs to be managed by international agencies in order to guarantee equal participation in the benefits by all (Boggio et al. 2020).[12] However, the declaration only calls for solidarity and international cooperation (art. 17–19 UDHGHR) – it expressly declares the human genome as common heritage solely "in a symbolic sense" (art. 1 UDHGHR), not in a legal sense, and the fact that there exists no binding instrument of international law speaks on the *opinio iuris* of states (Boggio et al. 2020; Deuring 2020[13])

Furthermore, the UDHGHR highlights the rights of individuals who are participating in biomedical research, such as informed consent and proportionality (art. 5 UDHGHR), non-discrimination (art. 6 UDHGHR), confidentiality of genetic data (art. 7 UDHGHR), as well as the right to indemnification for damages directly resulting from an intervention into their genome (art. 8 UDHGHR). It also calls for "respect for the human rights, fundamental freedoms and human dignity" (art. 12a UDHGHR; see also art. 10 and 11, as well as art. 25 UDHGHR) and defines the conditions under which research may be conducted (art. 12b–16 UDHGHR; Boggio et al. 2020; Yotova 2020).

2.2.2.2 UNESCO International Declaration on Human Genetic Data

To illustrate the dynamics between technological advancement and the law, the IDHGD was adopted (Boggio et al. 2020). In its art. 1, the declaration maps out its goal to be "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 … in keeping with the requirements of equality, justice and solidarity" as well as "to set out the principles which should guide States in the formulation of their legislation and their policies on these issues; and to form the basis for guidelines of good practices in these areas for the institutions and individuals concerned". Furthermore, the IDHGD calls on states to cultivate international cooperation and distribution of the scientific knowledge gained on human genetic data (art. 18 IDHGD).

11 These principles are the guide to the 2015 UNESCO IBC Report on genome editing.

12 Boggio et al. go on to highlight the paradox of the UDHGHR simultaneously recognizing the human genome as "individual to each" in art. 3; see in accordance with the idea of common "property" the contention that "the human genome, metaphorically speaking, belongs to all of us" (Baylis 2019, 44).

13 Deuring (2020, 33) calls it "normative neutralization", such that there is no real collective good in opposition to interventions to the germline.

2.2.2.3 UNESCO Universal Declaration on Bioethics and Human Rights

The UDBHR is broader than the two aforementioned UNESCO declarations: It deals, more generally, with the social, legal, and environmental implications of new technologies (art. 1 para. 1 UDBHR) and "provides guidance to decisions or practices of individuals, groups, communities, institutions and corporations, public and private" (art. 1 para. 2 UDBHR). Like the UDHGHR and the IDHGD, it emphasizes respect for human dignity, human rights and fundamental freedoms,[14] autonomy, and informed consent (art. 5 and 6 UDBHR), but for the first time, the international community expressed its desire to comply with the fundamental principles established (Boggio et al. 2020; see art. 3 para. 2–art. 17 UDBHR). In accordance with that, the declaration asks of states to promote "professionalism, honesty, integrity and transparency in decision-making" as well as dialogue and cooperation between experts and society in all its diversity (art. –18 para. 3, art. 19, art. 21, and art. 24 para. 1 UDBHR).

2.2.2.4 UNESCO Declaration on The Responsibilities Towards Future Generations

The DRTFG stresses in its art. 1 that "[t]he present generations have the responsibility of ensuring that the needs and interests of present and future generations are fully safeguarded", especially that humankind should be maintained and perpetuated, and the human genome protected with respect for human dignity (art. 3 and 6 DRTFG).

2.2.3 International Human Rights Law in Particular[15]

As has become apparent above, human rights are referenced recurrently in international hard law as well as soft law. Though international human rights law as it is now cannot adequately address germline genome editing, several human rights are of significant relevancy for genetic engineering (Yotova 2020), more specifically or as overarching principles.

The human rights most cogent to heritable genome editing are human dignity, the right to life, the right to physical and mental personal integrity, the right to health, the right to science and rights of science, as well as non-discrimination, the last finding its expression in the aforementioned. The rights of future generations (see DRTFG), while not a human right *per se,* are of critical importance as well (Yotova 2020).

14 Human dignity, autonomy and individual responsibility, respect for the vulnerable and for personal integrity, privacy and confidentiality, equality, justice and equity, non-discrimination and non-stigmatization, respect for cultural diversity and pluralism, solidarity and cooperation, social responsibility for health, sharing of benefits, protection of future generations and the environment, the biosphere and biodiversity (see art. 3 para. 1 and art. 10 UDBHR; UNESCO IBC 2015).

15 Arguably, one could assume that human rights law is not applicable due to the embryo not being under the protection of it, as its status as a person is not recognized (yet). However as noted above, germline genome editing in its "last form" aims at altering the DNA of an individual who will exist and be a subject of human rights law, such that this concern is not further addressed at this point (see also Yotova 2020).

2.2.3.1 Human Dignity

As proclaimed by art. 1 of the UN Universal Declaration on Human Rights (UDHR): "All human beings are born free and equal in dignity and rights." Dignity has a "founding function" for international human rights law (Dicke 2002) – the EU Charter, for instance, declares that "[h]uman dignity is inviolable" and that it "must be respected and protected" (art. 1 EU Charter). The Oviedo Convention includes it in its title and expressly proclaims the (very broad) protection of human dignity as its objective (art. 1 Oviedo Convention). Notably, there is no mention of dignity in the European Convention for the Protection of Human Rights and Fundamental Freedoms (ECHR) (Boggio et al. 2020).

Human dignity is more prominently featured in soft law instruments[16] than in traditional human rights law, meaning that it is not a directly legally binding standard. The value prescribed to dignity varies greatly amongst scholars and no legal instrument expressly and conclusively defines its scope (Andorno 2007; Boggio et al. 2020; Yotova 2020). However, dignity is acknowledged as the normative concept underpinning human rights in general (Yotova 2020), making it the "ultimate rationale" for regulation in the field of genetic engineering rather than an independent legal guarantee (Andorno 2007; Boggio et al. 2020; Yotova 2020). As such, human dignity a vital factor in the balancing of public interests and the rights of the individual, the welfare of which is a key concern in the context of heritable human genome editing (Yotova 2020).

The UDHGHR declares that humans shall be respected in their inherent dignity, but it is art. 2 para. b which sheds more light on what is meant by "dignity": Individuals must not be reduced to their genetic traits, as humans are not their germline (Boggio et al. 2020). This notion is perpetuated throughout the entire declaration (Boggio et al. 2019). The UDHGD and UDBHR both also repeatedly refer to human dignity (Boggio et al. 2020).

2.2.3.2 Right to Life

The right to life is codified in art. 2 ECHR and art. 2 of the EU Charter, as well as art. 3 UDHR. It is especially vital in answering questions pertaining to research on embryos that may be discarded in the process; however, it is still debated whether unborn life is warranted the protection of human rights (Deuring 2020).[17]

2.2.3.3 Right to Physical and Mental Personal Integrity

Art. 3 of the EU Charter provides for protection of the physical and mental integrity of individuals and prohibits eugenic practices. In a commentary on the EU Charter, the EU Network of Independent Experts on Fundamental Rights noted: "The protection of the embryo against genetic engineering and other unlawful

16 See above for the illustration of bioethics law.

17 Boggio and Yotova (2021, 960) argue that "gene editing of human embryos does not clash with the right to life …", but that genome editing instead reinforces the right to life.

research and the absolute prohibition of any modification in the genome of any descendants illustrates that the protection of the right to personal integrity extends to the unborn child and even to future generations." (EU Network of Independent Experts on Fundamental Rights Commentary of the Charter of Fundamental Rights of the European Union 2006, 39). While commendable and in tune with the general tone surrounding germline genome editing, this interpretation is not supported by the text of art. 3 EU Charter, and the bridging of the "gap between human rights protection and unborn children" using the concept of intergenerational equity is not widely accepted in practice (Yotova 2020, 670–671). Furthermore, it is important to note that the EU Charter is applicable only to member states implementing law of the EU (art. 51 para. 1 EU Charter), and the EU has only shared legislative competence in the field of public health.[18]

2.2.3.4 Right to Health

The right to health, first pronounced in the World Health Organization [WHO] Constitution, is a component of the right to an adequate standard of living articulated in art. 25 UDHR and is recognized in art. 12 of the International Covenant on Economic, Social and Cultural Rights[19] (ICESCR).[20]

While some authors recognize a "fundamental right to inherit a genome without deliberate manipulation" as part of the right to health, which would render germline genome editing on human embryos impermissible (Drabiak 2020, 227),[21] others contend that the right to health calls for states to "provide equality of access to a new technology" once its benefits and safety have been determined (Boggio and Yotova 2021, 960), thus defining the right to health from the viewpoint of equality and non-discrimination.

2.2.3.5 Right to Science and Rights of Science

Of especially critical relevancy to germline genome editing are the right to science (the right to enjoy the benefits of science) and the rights of science (e. g., the right to freedom of research, freedom to intellectual property and more) (Boggio et al. 2019; Boggio et al. 2020; Yotova 2020). The right to science, derived from the right to health (Boggio and Yotova 2021), is codified in art. 27 UDHR as well as art. 15 ICESCR. From it arise more distinct rights connected to scientific advancements and the application thereof (Boggio et al. 2019).

18 I. e., the member states may only enact laws if the EU has not done so or does not intend to legislate; see https://ec.europa.eu/info/about-european-commission/what-european-commission-does/law/areas-eu-action_en (accessed April 24, 2022).

19 Presently binding 171 state parties; see https://indicators.ohchr.org (accessed April 19, 2022).

20 See https://www.wma.net/what-we-do/human-rights/right-to-health/ (accessed April 25, 2022).

21 The question of whether embryos are protected by human rights poses itself here as well (see Boggio and Yotova 2021).

State parties of the ICESCR are to respect, protect, promote, and fulfill rights guaranteed (Leckie and Gallagher 2006). However, the normative content of the right to science has only been more closely investigated since over a decade ago, such that the relation of the aforementioned obligations to it has yet to be fully determined (Boggio et al. 2019; Boggio et al. 2020; Yotova 2020). In the Venice Statement, "respecting" has been interpreted as ensuring freedoms necessary for conducting science (autonomy, freedom of speech, respect of human rights etc.), "protecting" as employing means to protect the rights of individuals (e. g., research subject or vulnerable populations) and "fulfilling" as developing strategies like monitoring adverse effects, engaging the public in decision-making and securing non-discriminatory access (para. 14–16 Venice Statement). The Oviedo Convention also affirms the freedom of scientific research in its art. 15, though subject to the protection of human rights, meaning that freedom of research is not absolute (Boggio et al. 2020).

2.2.3.6 Rights of Future Generations

Although the rights of future generations are not a recognized traditional human right, the notion of protecting future progeny, mostly discussed in environmental law (Knoppers and Kleiderman 2019), is central in the context of heritable genome editing (Yotova 2020). It is expressed in the DRTFG as well as the UDBHR (art. 16) and the Oviedo Convention (art. 13 para. 1), and forms the base of the concepts of transgenerationalism and intergenerational equity, calling for the preservation of the interests of future generations in the process of technological advancement. Thus, applications of CRISPR should be considered with the welfare of the future persons in mind. However, some contend a "right to be corrected" or "not to be corrected" cannot be derived from the rights of future generations (Knoppers and Kleiderman 2019, 289).

2.2.4 Interim Conclusion

Human germline genome editing is, to a certain extent, already governed by international hard and soft law, i. e., there are widely acknowledged legal concepts and general principles applicable to it,[22] most notably those of international bioethics law and international human rights law.

International hard law is limited to mainly the Oviedo Convention, which provides rather clear-cut rules (a ban on heritable genome editing) and is legally binding, but has only been ratified by a few states in Europe. The Cartagena and Nagoya Protocols are more widely recognized and, accordingly, have been ratified by many states; however, they deal with genetic engineering in a more general sense.

22 Some highlight that "[y]et, such normative instruments form an important precedent" (Isasi and Knoppers 2015, 454).

The UNESCO declarations, albeit providing a general framework for tackling newly emerging biotechnology (particularly in the context of experimenting and further research) and certainly applicable to germline genome editing, fall short due to their lack of binding effect. While they shed light on the standards that could and should be implemented into the future policy governing heritable human genome editing, their language seems fairly vague and appear to only reiterate already well-established regulation and principles, e. g. those in the Declaration of Helsinki, the Council for International Organizations of Medical Sciences' Ethical Guidelines for Biomedical Research Involving Human Subjects, as well as best practices followed in the majority of developed states (Boggio et al. 2020).

The international human rights regime is well established and consistently upheld by states, but while it entails a number of human rights pertinent to germline genome editing, their scope and applicability in the context of heritable genome editing are not definitively determined.

In sum, the current regulatory framework applicable to heritable human genome editing is limited in jurisdictional reach and, in its substance, does not yet adequately address the contentious ethical and legal challenges that heritable human genome editing poses, as many questions specific to it are still left unanswered. Therefore, the regulatory pathway for germline genome editing requires considerable revamping.

3 Considerations for Future Global Governance

3.1. Preliminary Questions

3.1.1 Why Regulate?

A number of critics reject any kind of regulation of human germline genome editing for its potential undermining of reproductive rights and for fear of politicizing science, i. e., confusing science with moral values (Zaret 2016; Graves and Cook-Deegan 2019; EGE 2021).

Regarding the first concern, while the so-called libertarian view of reproduction falls short in recognizing the far-reaching implications of heritable genome editing, such as possible irreversible harm to the individual with edited DNA or the exacerbation of social inequality (Suter 2007; Zaret 2016; see NCB 2018 for an overview on all ethical considerations), the "reproductive *justice* framework" may offer more guidance, as it values reproduction as much as it encourages attentive and inclusive deliberation on "how public policy regarding reproduction can promote well-being, equality, and diversity" without concluding once and for all if and how regulation should be imposed (Zaret 2016, 1834–1836; see Ross 2008 for more on reproductive justice in the context of the pro-choice movement).

As to the second concern: Rejecting limitations on genome editing technologies by a regulatory framework based on the contention that facts and morality are not to coincide simply renders impossible any deliberation on how human germline genome editing may be applied responsibly and does not give any substantive answers. Moral values are inescapably tied to policies governing reproduction (or science, for that matter; EGE 2021, 23[23]), and admittedly, it is true that more vulnerable groups of people may be overlooked in shaping the regulatory framework because political actors involved in legislation, though very influential, are often more distanced from the issue than those who are really affected (Peterson 2012; Zaret 2016; Cashore et al. 2021; Xafis et al. 2021).[24] This, however, is precisely the reason why it is paramount that human germline genome editing is regulated on the basis of democratic considerations of "broadly inclusive of groups who will feel the practical effects of law limiting this technology" (Zaret 2016, 1836–1837; Weller et al. 2021) and not governed by the facts of science alone (Darnovsky 2009, 38, calling this approach "biopolitics").

3.1.2 Why International Regulation?

Although heritable genome editing is, for the time being, still banned in most countries (Knoppers and Kleiderman 2019), an appropriate and *shared* ethical and legal framework ought to be developed within a sensible timeframe. Even if clinical applications of CRISPR seem to be a distant reality (Mulvihill et al. 2017; Coller 2019; Liu 2020; Townsend 2020; Piergentili et al. 2021), the question seems to no longer be that of "if" (Stock and Campbell 2000; Araki and Ishii 2014; NCB 2018; Odzuck 2018; Tomlinson, 2018; CCNE 2019; Greenfield 2019; Halpern et al. 2019; Niemiec and Howard 2020)[25], and the current legal systems are overwhelmed in trying to keep up with the CRISPR revolution (Boggio et al. 2019). Domestic laws governing a specific technology are often practically ineffective and predetermined to be eclipsed by scientific advancement, as legislatory processes tend to lag behind the sciences; furthermore, they often allow for loopholes due to lack of clarity (Isasi and Knoppers 2015; Kaan et al. 2021). The extraordinary potential of CRISPR as well as the possibility of its abuse call for a comprehensive reform of its regulatory pathway (Boggio et al. 2019; Yotova 2020), given that effective regulatory oversight is considered a prerequisite for investment and innovation (Zaret 2016; Tomlinson 2018; see also Pugatch Consilium 2015), which are necessary to further assess the technology. Though biotechnology can be governed by national laws, the establishment of *global* standards for the governance of heritable genome editing is vital (Charo 2016; CCNE 2019; Coller 2019; Yotova 2020), especially since

23 Pointing out that "determining what is 'safe enough' is not only about knowledge, but also about values, and scientific theories and practices are themselves value-laden".

24 The same goes for scholars debating the issue (see Veit et al. 2021).

25 Andorno et al. 2020, however, urge to the contrary, insisting that the question of "if" has yet to be answered.

it may affect all of humanity (Araki and Ishii 2014; NCB 2018; Odzuck 2018; CCNE 2019; Greenfield 2019; Halpern et al. 2019; Niemiec and Howard 2020). Providing overarching uniformity and equality in how CRISPR is used in this context will aid in mitigating possibly grave impacts on future generations and social justice as well as help prevent ethics dumping and medical tourism (Mulvihill et al. 2017; Baylis et al. 2020; Yotova 2020; Napoletano et al. 2021; Xafis et al. 2021; see Béland and Zarzeczny 2018 on medical tourism in general).

The main concerns surrounding the appropriate use of CRISPR to alter the human germline should thus be addressed proactively by way of reaching consensus in the course of broad public debate (Gorgoni 2018; Tomlinson 2018; Gabel and Moreno 2019; von Hammerstein et al. 2019; NAS 2020; Yotova 2020). International law offers the necessary processes to form and implement this consensus, and, as shown above and discussed in the section on the Human Rights Approach below, provides for the "tools necessary to balance the welfare of the individual with the interests of humanity as a whole" and binds states as well as non-state actors (Yotova 2020).

Achieving the goal of effective international governance of human germline genome editing requires close examination of several questions: (1) Is reaching a consensus even possible (Tomlinson 2018; Morrison and de Saille 2019[26]) and if so, how? (2) Assuming a consensus is achievable, how can a comprehensive, binding but flexible regulatory framework be established, i. e. what kinds of vehicles can be employed to make sure it accurately reflects international moral, cultural, and legal standards on a continuous basis (Molnár-Gábor 2018; Yotova 2020[27])? (3) How can compliance therewith be monitored and its enforceability ensured (Charo 2016; Molnár-Gábor 2018; Rixen 2018; Baylis et al. 2020)? And lastly (4) who assumes the responsibility for the demanding task of initiating and continuing the process?

3.2 Consensus-Building: Engaging the Public with Science and Policymaking

3.2.1 Consolidating Different Consensuses: Participatory and Inclusive Debate

It seems that there are different consensuses on human germline genome editing that will have to be consolidated in a legal framework:[28] The political consensus, the scientific consensus, and the societal consensus. The first tends towards

26 Urging to "engage robustly with what is meant by 'consensus' and how we will know that it has been achieved".

27 Noting on p. 661 that we will need to re-evaluate current legal instruments and that there is the "need for new and effective international regulation".

28 As noted by Feeney (2019, 242), Resnik and Vorhaus (2006, 9) already pointed out in 2006 that the discussion will soon "move outside the world of academia into the world of public policy and political decision-making". Gorgoni (2018, 262) emphasizes that as long as scientific uncertainty "affects some essential aspects of our societies, the scientific and political debates become intertwined".

prohibiting heritable genome editing, or at least imposing a moratorium. This is reflected in the many bans placed by national laws, the Oviedo Convention, art. 13 of which prohibits interventions in the human genome to "introduce any modification in the genome of any descendants", as well as the UNESCO IBC Report from 2015. The scientific "consensus", on the other hand, varies strongly, with some scientists arguing for a moratorium and others favoring a more forward-thinking approach (Brokowski 2018, 117–119 for an illustration in tables; Veit et al. 2021, 66[29]). As discussed in section 3.3.2, even the two most prominent recommendations published by the National Academy of Sciences (NAS) and the Nuffield Council on Bioethics (NCB), agree on heritable human genome editing being admissible under certain conditions, but diverge in their stipulations. Things get even more complicated when it comes to the societal consensus – while some authors still refer to the requirement of "broad societal consensus" (Gorgoni 2018; Tomlinson 2018; Gabel and Moreno 2019; von Hammerstein et al. 2019; NAS 2020; Yotova 2020) that was expressed at the 2015 International Summit on Human Gene Editing (even though the language was much different in the 2018 summit statement), others contend that reaching a global consensus is "simply impossible" (Baylis 2019, 42). Notwithstanding this judgment, its significance and breadth are being examined more thoroughly and cannot be categorically denied (Brokowski 2018; Baylis 2019; Veit et al. 2021, 65[30]).

Undoubtedly, it will be extremely difficult to reach a final consensus on how to regulate human germline genome editing, seeing as though we live in a multicultural world society comprised of sovereign states (Charo 2016; Dabrock 2018; CCNE 2019; Gyngell et al. 2019; Krekora-Zajac 2020; see Xafis et al. 2021, 4–6, on the "national interest lens"). Though there are usually no generally accepted sources of moral judgments (Rixen 2018; Halpern et al. 2019; Townsend 2020), matters of public policy usually require a conclusion on any given debate (Trotter 2001, 45[31]; NCB 2016; Araújo 2018; Meagher et al. 2020). In morally plural societies (Dabrock 2018), reaching consensus on matters of public policy is generally a political activity (Charo 2016; NCB 2016; Dabrock 2018; Gyngell et al. 2019) and this goal may be attained only gradually (Mulvihill et al. 2017, 20; Andorno et al. 2020; Boggio et al. 2020), as "disruptive technologies are also social phenomena that are subject to rapid and constant transformations" (Mulvihill 2017, 20). While democratic governance appears to provide for a procedurally legitimate solution to contentious issues, such processes are slow, inflexible, difficult, and

29 Veint et al. point out that "academic polarization is just as real as political polarization and can undermine careful reflection when we are faced with complex ethical problems" and advocates for interdisciplinary and, most of all, attentive dialogue without "turning this issue into a semantic debate" (2021, 66).

30 Justly Veit et al. emphasize out that we have to exit our "echo chambers" (2021, 65).

31 Trotter (2001, 45) proposes for the concept of "moral compromise" to be considered in place of consensus, although there are critics of this notion (see Trotter 2001, 46–47).

costly (Charo 2016; NCB 2016; Cavaliere 2018[32]; Kaelin 2018; Cashore et al. 2021), in turn conceivably stifling innovation and research (Graves and Cook-Deegan 2019; Bilir et al. 2021). However, given the stakes at play and possibilities available to support scientific progress, it is imperative that all stakeholders take part in a thorough discussion pertaining to research on heritable genome editing and clinical applications of the CRISPR technology (NCB 2018; CCNE 2019; Halpern et al. 2019; Baylis et al. 2020; NAS 2020; Townsend 2020; Yotova 2020).[33] Although some authors question the sincerity of the call for "public engagement with science" (Dabrock 2018, 176),[34] it will ease the public's concern of transformative technology rushing ahead of its scrutiny (Mulvihill et al. 2017; Tomlinson 2018; Halpern et al. 2019; Weller et al. 2021). Furthermore, multi-faceted deliberation on the topic can address the risk of path dependency by offering a platform where alternatives to new technologies can be explored (NCB 2016; NCB 2018).

Engaging citizens in evaluating newly emerging technology, though essential in this case, is not a simple task and appropriate methods need to be established (Arnaldi 2018). Participation alone does not guarantee a reasonable outcome – the quality of the decision depends particularly on the composition of participants, their means of participation, and the link between the participation and the decision-making process (Gianni 2016; see also Graves and Cook-Deegan 2019). One tool for involving the public in decision-making about future regulatory frameworks for new technologies worth noting is a method called the pTA, short for "participatory technology assessment". It is specifically designed to enable open dialogue between "experts" in a field and a broad spectrum of citizens (i. e., not only prominently represented groups) "to gain insights into public policy dilemmas involving science, technology, and uncertainty" and to provide them the "opportunity to see other views from the standpoint of differing values rather than as 'right' or 'wrong'" (Weller et al. 2021, 12). In many cases, members of the public have expressed concerns, values, and alternatives that were not prioritized by experts, be it consciously or subconsciously (Weller at al. 2021). The recruitment of a diverse group, intense engagement with stakeholders prior to a gathering, and a rigorous structure for mapping out the core issues and values (e. g., use of focus groups) allow for conversations in which mutual perspectives as well as new concepts can be discussed. Based on these conversations, educational content is developed to summarize them and invite people to further deliberate on the topic

32 Cavaliere 2018, 210–218 offers different methods that could be considered to "argue about new technologies".

33 Additionally, see art. 28 of the Oviedo Convention, prescribing the prerequisite of "appropriate public discussion" on the "fundamental questions raised by the developments of biology and medicine".

34 Meagher et al. (2020, 335) conclude that consensus "is not a requirement for creating more appropriate research ethics policies"; Xafis et al. (2021, 10) conclude that "calls for broad societal consensus neglect structural injustice".

(Jasanoff et al. 2015[35]; Baylis 2019, 44[36]; Weller et al. 2021). A similar approach may be implemented locally and expanded to a higher level, e. g. put into the hands of the interdisciplinary Global Genome Editing Observatory (Jasanoff and Hurlbut 2018; EGE 2021; similarly Schleidgen et al. 2020) or the WHO or UNESCO (Yotova 2020).[37] For the moment, this institution is tasked with gathering representatives and information on genome editing in order to support the progress in assessing the technology,[38] and thus would lend itself well for consensus-finding processes.

3.2.2 Reexamining Established Legal Concepts

A prerequisite to effectively regulating human germline genome editing will be the reevaluation of foundational legal concepts during the consensus-finding process, especially reconsideration of current notions of autonomy and the legal (and moral) status of embryos, with that the already well established theory of informed consent, as well as equality and non-discrimination.[39]

In the context of heritable human genome editing, questions regarding autonomy and informed consent are especially prominent and pressing, since a person and their offspring may be subject to an irreversible modification of their genetic makeup without having been able to consent to it and all the consequences of the intervention (Smolenski 2015; Rubeis 2018; Coller 2019; Halpern et al. 2019; Niemiec and Howard 2020) and thus their autonomy may be violated (Brokowski and Adli 2018; Dabrock 2018; von Hammerstein et al. 2019). Can parental rights, for example, be extended to encompass such a decision in place of the prospective generations (Evitt et al. 2015[40]), or is the aim only to treat the parents' infertility and not the hereditary disease, rendering the children's consent obsolete (Krekora-Zajac 2020)? Some authors deny such a parental right to proxy consent, at least for the time being (Smolenski 2015[41]; Montoya 2020 for the U. S. context; Ishii 2021), while others contend that the "autonomy of embryos" is illusory and does not warrant moral protection, suggesting that "regulators should be on whether an

35 Jasanoff et al. (2015) criticize the tendency for members of civil society to be dismissed for lack of expertise in the science behind new technologies even though their opposition stems from different ideas, depriving them of "the freedom to decide what forms of progress are culturally and morally acceptable".

36 Baylis (2019, 44) calls for empowerment of civil society instead of conclusions imposed by the scientific community and points to how the dynamics of inclusive consensus-building differ from the workings of consensus-building processes where only experts or people of power are involved.

37 More about the responsibility to regulate in the section "Who is Responsible?".

38 See https://global-observatory.org/about/ (accessed December 12, 2022).

39 This is just to name a few – there are many other important substantive questions that arise, though a lot of them are strongly interwoven and can hardly be answered independently.

40 It is to be noted that while posing this question Evitt et al. (2015) recognize that a higher standard is necessary due to the risks of the edit.

41 On the grounds that genetic edits are irreversible and unjustifiable speculation is involved, especially considering the uncertainty about the safety of human germline genome editing using CRISPR.

object of research exhibits actual, rather than potential, morally relevant properties" (Piotrowska 2015, 177). Some authors assume an "intermediate moral status between nonhuman life and a fetus" for embryos (Evitt et al. 2015, 26). Neither does the so-called escape clause, allowing subjects to withdraw their consent for participation in a research project, solve this issue adequately because the edit in their DNA will likely be irreversible (Smolenski 2015).[42]

Ultimately, human germline genome editing needs to be analyzed in the light of the interests of the person to be, since the purpose of it is, precisely, to bring upon a human being that *will* exist and have to live with all the ramifications of the edit.[43] Therefore, since there are no ways to obtain informed consent as we know it today from future persons, new ethical and legal frameworks for multigenerational consent (Coller 2019),[44] as well as legally recognized bearers of rights (Pfeffer Billauer 2020, on legal fiction and, at pp. 43–45, on pre-conception injury; Yotova 2020) need to be developed should we aim to start conducting research and apply CRISPR clinically to alter human germline DNA. Alternatively, regulators could require a reversal strategy to undo the edit should the person wish to do so (Evitt et al. 2015).

The rigorous research required prior to clinical applications (CCNE 2019; Baylis et al. 2020) also raises questions about the undue instrumentalization of human embryos and the moral contentions to creating them for research purposes, which are still heavily debated (Araki and Ishii 2014; Baylis et al. 2020; Koplin and Gyngell 2020; Niemiec and Howard 2020).

One additional aspect to consider is the (social and legal) liability for human germline genome editing going amiss (Rodriguez 2016; Jonlin 2020) – shall victims be entitled to claims against a practitioner in a case of wrongful birth damages (claimed by parents) or wrongful life damages (claimed by the person whose DNA has been edited)? And if so, who would assess such claims? Demonstrating a direct cause of a disability by an off-target effect may not be feasible. In some jurisdictions, wrongful life suits have been rejected altogether. In any case, both the parents consenting to an edit and the practitioner will have to assume responsibility for their decisions and actions (Yotova 2020; Ishii 2021; for a

42 Unless, of course, scientists manage to develop a reliable reversal process.

43 This applies already to research on heritable human genome editing, as at least for now, examining the effects of such technology would have to entail the birth individuals and the documentation of the effects the edit has on them (see e. g. Drabiak 2020). It is worth mentioning at this point that the fact that the purpose is to edit the DNA of a person that will live also lets us sidestep the "non-identity" problem, i. e., the dilemma of arguing for the interests of a person who, had a different course of action been taken, would have never existed (see von Hammerstein et al. (2019), as well as Omerbasic (2018, 74–78), concluding the same, however going on to differentiate between the embryo born and the next generation and suggesting a supplementary notion of "non-person-affecting harm principle" at; Rubeis (2018) disagrees).

44 See Fateh-Moghadam (2018), discussing autonomy and informed consent and its relation to transformative technologies on a more general level, and concluding that questions concerning autonomy in the era of biotech can only be solved in an intra- and interdisciplinary fashion.

general overview on wrongful birth and wrongful life suits see Frati et al. 2017 and Pfeffer Billauer 2020).

This uncertainty in the allocation of responsibility within the existing concept of liability may result in prohibitive policies that could crack down on research (Baylis et al. 2020; Ishii 2021) and have a negative effect on the self-regulation of the scientific community (Gorgoni 2018). Most importantly, such policy-making may impact individuals who suffer damages resulting from the edit to their detriment (Krekora-Zajac 2020).

On the innovation end, the question of patentability of genome editing further complicates things, as patents can direct investment in specific research areas (WHO Framework 2021). EU regulations generally disincentivize research on genome editing with restrictive policies that are disconnected from the industry and by declaring it non-patentable. Funding for research on germline genome editing is expressly prohibited (Horizon Europe) and such practices outlawed by the Oviedo Convention all together (Dodai et al. 2021; art. 13 Oviedo Convention). A stark contrast to that is the regulation in the U.S., though a "complex competitive environment that could last for years has developed, perhaps diverting focus from benefiting the public good" and that could have a stifling effect on research as well as access to genome editing technology (Rodriguez 2016; Mulvihill et al. 2017, 21–22, referencing Ledford 2016). Thus, regulators should strive to strike a reasonable balance between intellectual property law and boosting innovation as well as equitable access to the benefits of the technology.

3.2.3 Interim Conclusion

A wide array of stakeholders should prioritize establishing a process and forum for a broad public debate on heritable human genome editing to determine whether it is admissible under ethical viewpoints. Simultaneously, relevant legal concepts currently established should be reevaluated against the backdrop of the very specific challenges germline genome editing poses. The pTA could be a useful tool to consolidate the diverging viewpoints and facilitate inclusiveness in order to achieve a differentiated outcome of the debate. The foregoing paragraphs highlight only a fraction of notions requiring reevaluation – broader society and policymakers will need to ask themselves and attempt to resolve many complex questions of ethics and law before practicing human germline genome editing can be seriously considered.[45] Many authors have called for a moratorium on human germline genome editing to be imposed in the meantime (UNESCO IBC 2015; Kaan et al. 2021, 3[46]; Knoppers and Kleiderman 2019 to the same effect).

45 Darnovsky (2009), for instance, expresses concerns about the fact that fertility clinics are largely unregulated, which could incentivize parents to take unnecessary risks or medical professionals to engage in unethical practices such as enhancement.

46 Kaan et al. (2021, 3) point out the drawbacks of a moratorium, such as the risk of it resulting in "another ineffectual political express of intent", the "bottom-of-the-barrel" scenario where scientists

3.3 Potential Approaches to Policymaking and Available Legal Instruments

Policymakers can employ a multitude of instruments, institutions, and procedures to govern heritable human genome editing until and after it is deemed permissible (WHO Framework 2021). In order to stay within the ambit set out for this paper, the following analysis will be limited to the general categories of hard law (international agreements), soft law, and one possibility of a compromise between to two (the human rights approach).

3.3.1 International Agreements

One possibility in building a regulatory framework to govern CRISPR and human germline genome editing would be to make use of already established agreements by updating and coordinating them accordingly (Brokowski 2018; Brokowski and Adli 2018). Animating the global community to enact policies on germline genome editing by way of adjusting international agreements that are already in place may strengthen their position and thus augment their efficacy to mitigate the problem of enforceability that arises with soft law (Tomlinson 2018; WHO Framework 2021), as states ratifying the agreement will clearly express the will to be bound by the policy envisioned and be held accountable for implementing it.

The Oviedo Convention, already reflecting in large part the principles which most authors consider to play an imperative role in heritable human genome editing, comes to mind, though it would have to be substantially amended should such ventures be deemed permissible (especially art. 13 and 18, or the provisions dealing with informed consent). The Cartagena Protocol and Nagoya Protocol both sport a large number of state members and are viable options for modernization (Tomlinson 2018). Alternatively, a new treaty could be negotiated (WHO Framework 2021).[47]

However, a myriad of hurdles presents itself when considering substantially modernizing existing international agreements or negotiating a new treaty to govern germline genome editing. The first and probably the most important caveat is that it is exceptionally demanding and time-consuming to integrate social, political, and ethical norms of different states into a single regulatory regime (Pauwelyn et al. 2014; Tomlinson 2018; Kaan et al. 2021). Consequently, using vague language to capture a minimum of consensus is practically inevitable (Boggio et al. 2020), and the content may already be overridden by the time signatories have ratified the treaty (Kaan et al. 2021), which may lead to ineffective governance. Another concern (though arguably present in any attempt to regulation) is that countries or practitioners with malicious intent are unlikely to comply with the stipulations of

simply move to more liberal countries, as well as a possible chilling effect.

47 Though countries bound by the Oviedo Convention will have to sever their ties to it, as it expressly prohibits editing of the human germline, to join a possibly more permissible treaty. Amending the Oviedo Convention would be a possibility, but requires the consent of its parties and a more extensive negotiation process (see art. 32 Oviedo Convention).

the treaty, irrespective of how comprehensible the regulation may be (Tomlinson 2018; Kaan et al. 2021; Xafis et al. 2021 on national interests). Additionally, one must keep in mind that the development of an international regulatory system requires a significant amount of resources which will in turn be unavailable for the implementation of effective oversight on a domestic level (Tomlinson 2018; WHO Recommendations 2021). Furthermore, international agreements are not flexible and thus may not be able to accommodate for the fast-paced changes in biotechnology (WHO Framework 2021).

A factor to consider with regards to enforceability of current hard law in particular is that a large number of parties that have ratified the treaties are middle- to low-income states which may not be capable of effectively enforcing the regulation put in place. Moreover, countries with high-profile research on CRISPR, notably the U.S., are not signatories (Tomlinson 2018[48]) which might be problematic, as treaties only bind states and international organizations that have ratified them (Boggio et al. 2020). Finally, the jurisdictions of the Cartagena and Nagoya Protocols are not expansive enough to cover new biotechnology (Boggio et al. 2020).

3.3.2 Employ Soft Power

In the face of the difficulties that may be encountered in revamping existing international agreements, some experts are advocating for transnational governance using soft power concepts (Tomlinson 2018; Kaan et al. 2021).

In addition to the UNESCO Declarations described above, a number of non-governmental and intergovernmental institutions have been publishing statements, recommendations, or policy papers focused on human germline genome editing (Boggio et al. 2020; Yotova 2020; Kaan et al. 2021) that may provide a basis for developing international standards governing it (Brokowski 2018; Brokowski and Adli 2018; Boggio et al. 2020; Piergentili et al. 2021).[49] 54 percent of them explicitly deemed it impermissible at this point in time, 11 percent agreed but acknowledged exceptions under certain conditions, 30 percent remained cryptic or undecided and only a mere 5 percent conveyed openness to further examining CRISPR and human germline genome editing as per 2018 (Brokowski 2018). However, the stances may shift gradually along with technological advancements and the opinion of the broader public (Boggio et al. 2020).

While the biggest downfall of soft law instrument is the fact that they are not legally enforceable and often tentative in language, they nevertheless play an increasingly important role because policies originating from soft power are based

48 Quoting NAS (2016, 154), where it is pointed out that the U.S. "does not have a clear policy for collaborating with other countries with divergent systems of governance".

49 See section "Soft Law (International Bioethics Law)" above.

on discretion and cooperation.[50] Moreover, they are responsive to technological advancements and cultural change, as more suitable interpretations can be adopted fairly quickly (an advantage inherent to equivocal terminology). This facilitates commitment of states that may not have ratified a binding treaty entailing the same provisions (Pauwelyn et al. 2014). Furthermore, newly emerging actors can participate in regulation and offer expertise on this very complex topic (Pauwelyn et al. 2014; Kaan et al. 2021[51]) and multiple approaches can be assessed concurrently and progressively built up to be more stable mechanisms for oversight.

In the following, the recommendations from four widely acknowledged institutions, which could inform the regulatory both procedurally and substantively, shall be highlighted: The UNESCO IBC, the WHO, the NAS, and the NCB (de Lecuona et al. 2017 and Brokowski 2018 for a general overview). Despite earning some criticism for not offering justifications for limiting human germline genome editing or outlining structures for the public debate they nearly universally call for (Brokowski 2018; Boggio et al. 2020), these recommendations are not to be easily dismisse – considering the complexity of the topic, it would prove difficult for governments to justify straying from them (Boggio et al. 2020). In addition, if followed consistently and considered as *opinio iuris*, these stipulations may in turn eventually become hard law in the form of customary international law (Pauwelyn et al. 2014, 749[52]; Isasi and Knoppers 2015; Zaret 2016, 1832[53]; Boggio et al. 2020, 26[54]).

3.3.2.1 Recommendations from the UNESCO IBC

The UNESCO identifies nine characteristics of "good governance": accountability, transparency, responsiveness, adherence to the rule of law, stability, equity, inclusiveness, empowerment, and broad-based participation.[55] In its 2015 report, the UNESCO International Bioethics Committee (IBC) updated its considerations on human genome editing and human rights. It identifies the five ethical principles that guide its reflection on the technology: Respect for autonomy and privacy; justice and solidarity; understanding of illness and health; cultural, social, and economic context of science; responsibility towards future generations. Based on these principles, the IBC calls for a moratorium on germline genome editing

50 To avoid redundancies: This is strongly linked to self-regulation, which is discussed below section covering the human rights approach and the freedom of research.

51 Kaan et al. (2021, 5) point out the disadvantage of traditional lawmaking involving only politicians, who are "usually also far removed from the actual experience and practice of the science involved".

52 Speaking of "thick stakeholder consensus" where more actors than only states are involved in international lawmaking.

53 Zaret (2016, 1832) highlights the importance of flexibility of legislation in the face of transformative technologies and changes in society's view of them.

54 Boggio et al. call soft law "customary international law in the making", i. e., developing hard law (2020, 26).

55 See http://www.ibe.unesco.org/en/geqaf/technical-notes/concept-governance (accessed April 23, 2022).

until the safety and efficacy of CRISPR have been assessed; until then, states shall contribute towards a global standard with the UNESCO Declaration on the Human Genome and Human Rights as a basis and in collaboration with the scientific community, the media and educators as well as economic actors. Furthermore, the IBC suggests that the UNESCO Declarations be revised in terms of their application in this new context (UNESCO IBC 2015).

3.3.2.2 Recommendations from the WHO

The WHO pursues the goal of attaining the "highest possible level of health" through three "core functions": The normative function (i. e., drafting treaties, regulations, and non-binding recommendations), direction and coordination, as well as research and technical cooperation (art. 1 and 2 WHO Constitution). However, until recently, the WHO has not been very active in adopting legal instruments pertaining to genetic research in general, much less to human genome editing, and has instead focused on supporting genomic research through its two latter functions, i. e., through direction and coordination as well as research and technical cooperation (Boggio et al. 2020). In 2018, the WHO put together a panel of experts to evaluate a potential international standard for heritable human genome editing and has since published its recommendations, in which it recognizes its "essential role to play in helping negotiate and promote norms and regulations that can ensure our most important values will guide the application of genome editing technologies" and its unique position "to articulate global ethical values" and "exercise moral authority" (WHO Recommendations 2021, 3 and 5). It expresses its obligation to support the process to achieving effective governance, but makes the reservation that it can only do so in the short term due to a lack of resources (WHO Recommendations 2021). Though the WHO emphasizes the need for international collaboration, as there is currently not one institution that can bear the responsibility for the governance of human genome editing, it contends that it "cannot mandate a coordinated global approach", instead suggesting the UNESCO or the OECD (WHO Recommendations 2021, 5–6 and 7).

The WHO takes inspiration from the overarching criteria of "good governance" of public affairs stipulated by the UNESCO (WHO Framework 2021, 10). In doing so, it highlights the ethical values and principles applicable in the context of human genome editing, identifies good practices in public engagement, as well as the challenges that will have to be addressed should we aim to practice heritable genome editing.

In August 2019, the WHO has launched the "global human genome editing registry" to collect data in order to grant public access to it as well as monitor uses of CRISPR (WHO Recommendations 2021, 8). Though focused on somatic genome editing and in need of substantial expansion in terms of ensuring the legitimacy of applications of CRISPR (i. e., implementation of ethical approval), the WHO

suggests that it include data from future germline genome editing, should it be authorized (WHO Recommendations 2021).

3.3.2.3 Recommendations from the NAS

The NAS have identified seven governance principles overarching the future regulation of heritable genome editing: promoting well-being, transparency, due care, responsible science, respect for persons, fairness, and transnational cooperation (NAS 2017). According to the NAS report, a "robust and effective regulatory framework" would entail a number of stipulations (NAS 2017, 7–8): That (1) there be no reasonable alternatives to the trial (see also EGE 2021);[56] (2) the goal of research be the prevention of serious diseases or disabilities;[57] (3) the research focus only on genes predisposing or causing the disease or disability; (4) the modification be aimed at restoring health and be unlikely to have adverse effects; (5) there be adequate data available; (6) there be ongoing surveillance of the health and safety of individuals participating in clinical research; (7) there be long-term follow-up plans in place; (8) transparency and protection of privacy be ensured; (9) there be controls over societal risks; and (10) that there be mechanisms in place to prevent misuse for untenable causes. However, the NAS have not elaborated as on why or how they limitations are justified (Brokowski 2018).

3.3.2.4 Recommendations from the NCB

In its report from 2018, the NCB notes that human germline editing is neither therapeutic nor preventative of diseases in a traditional sense (NCB 2018). Instead, it ought to be considered as a means to fulfill reproductive desires, thus as infertility treatment (NCB 2018; Rubeis 2018). Adopting this viewpoint shifts the focus in the evaluation of the risks and benefits of heritable human genome editing and potential clinical applications of it (Rubeis 2018) to (reproductive) autonomy (Rubeis 2018[58]; Yotova 2020). As mentioned before, this leads to difficult questions about informed consent and balancing of individual and public interests (Yotova 2020).[59] This is not to say the NCB ignores these limitations; it explicitly

56 Andorno et al. (2020, 352) argue that "parents at risk of transmitting a genetic condition already have several options to avoid doing so", e. g., by using preimplantation genetic diagnosis.

57 Similarly, but more restrictive Schleidgen et al. (2020, 11) name treatment and prevention of serious and "incurable hereditary diseases" as a stipulation.

58 Though Rubeis (2018) does not believe that such argumentation will be sufficient to justify germline genome editing, because it is largely considered to be a negative right (i. e., a right protecting from state interference), as opposed to a positive right (i. e., a right stipulating the duty of the state to actively provide for the circumstances facilitating the exercise of the right).

59 See above in the section "Why Regulate?" where the libertarian view of reproduction is discussed briefly.

highlights that the genetic intervention needs to be in line with the welfare of the future child,[60] as well as social justice and solidarity (NCB 2018).

3.3.3 A Compromise: International Human Rights Approach

Given the disadvantages of employing either hard law or soft law to regulate germline genome editing, a compromise of the two may be the most favorable approach (Schiff Berman 2007; Pauwelyn et al. 2014; WHO 2021a). Some authors propose an international human rights approach to regulating human germline modification (Boggio et al. 2020[61]; Yotova 2020).[62] They argue that other bioethics instruments only "provide a narrow and inadequate account of the range of human rights that must be taken into account in this global conversation," and thus must be "integrated with the broader international human rights law corpus" (Boggio et al. 2020, 72 and 78; see also Yotova 2020[63]). As established above, as opposed to the legally binding international human rights treaties and human rights standards widely adhered to as customary law, bioethics law (while often referencing human rights) is for the most part soft law (Boggio et al. 2019; Boggio et al. 2020). International human rights standards have proven their legitimacy in the international community (Isasi and Knoppers 2015) – they are "the legal articulation of widely agreed upon values" and an "expression of an internationally negotiated consensus" (Boggio et al. 2019, 134–135).[64] Though they cannot adequately address all aspects of germline genome editing, they may still offer a solid foundation upon which future regulation can be built (Yotova 2020). Soft power instruments on the other hand foster more readiness, cooperation, and flexibility while exhibiting potential of eventually becoming established law.[65] Furthermore, the soft law instruments (be it bioethics law or the more target-oriented recommendations discussed above) often stress the importance of adherence to human rights, facilitating their convergence. Such an approach, in taking the best of both worlds, may mitigate the downsides of regulation through international treaties or through soft law alone (Yotova 2020) and may leave room for the different views on germline genome editing which still diverge significantly (Boggio et al. 2020).

The five core principles of the newly integrated framework, as suggested by authors favoring the international human rights approach, are: Freedom of

60 This significantly broadens the range of possible applications of CRISPR (see Gyngell et al. 2019, 517); Yotova (2020, 665) correctly points out that the welfare of the individual is an "ethical concept which is not legally defined".

61 Though they contend that states should be regulating heritable genome editing, not international organizations or civil society.

62 See Boggio and Yotova 2021 regarding the applicability of human rights law to embryos.

63 Though faulting the international human rights regime as well.

64 Visit https://indicators.ohchr.org (accessed April 19. 2022) for an interactive showing of the ratification statuses for international human rights treaties.

65 See above in the chapter "Employ Soft Power".

research,[66] benefit sharing, solidarity, respect for dignity, and obligation to respect and protect the rights and individual freedoms of others. To successfully implement these principles, states must create a suitable environment for cooperation through laws, regulations, and funding (Boggio et al. 2019; Boggio et al. 2020).

3.3.3.1 Freedom of (Responsible) Research and Self-Regulation

In order to sufficiently explore the potential of CRISPR in human germline genome editing, the scientific community needs to enjoy freedom of research while simultaneously being mindful of their responsibility to respect the core principles applicable to such activity (Boggio et al. 2019; see also art. 4 ICESCR).

Several international instruments recognize freedom of research, e. g., the ICESCR ,the Oviedo Convention, as well as the UNESCO Declarations mentioned above. Importantly, the latter entail the right of the scientists to self-regulate through customs, principles, norms, and institutions (all soft power elements) – a right that is cardinal to the constitution of the scientific community and to responsible science (Boggio et al. 2020), especially when there is no particular policy in place (WHO 2021a). Self-regulation encompasses "adherence to the scientific method, timely communication and publication, refinement of results through replication and extension of the original work, peer review, data sharing, authorship, and training and supervision of associates and students" (Boggio et al. 2020, 74; see also Mulvihill et al. 2017 and Bilir et al. 2021). Considering the exponential speed with which genome engineering technology is advancing (Smolenski 2015), effective self-regulation within the scientific community (Smolenski 2015; Charo 2016; Meagher et al. 2020; see also Grabs et al. 2021 on private regulation from a methodological viewpoint) in addition to institutional supervision (Charo 2016; CCNE 2019; NAS 2020 with several suggestions and recommendations) will be of primary importance. Self-regulation is suggested not to circumvent regulation itself, but because it can act as a buffer until a consensus on how to proceed with germline genome editing has been reached as well as support the future regulatory framework once it is in place (Courtright-Lim 2022). It contributes to deterring from improper conduct as well as fostering the trust of the public in professionals in the genome editing field. Several established guidelines can be used as reference points (WHO 2021a). Institutional supervision, on the other hand, is vital because self-regulation alone can entice scientists to recklessly push boundaries (van Beers 2020).

States must not limit the rights of science without justifiable grounds, e. g. welfare in a democratic society, and must meet the proportionality standard (see art. 4 ICESCR), so that absolute forms of regulation (i. e., no regulation at all or a complete ban without weighing of the interests at play) would not be permissible

66 See the discussion of the right to science and rights of science in the above section "Human Rights Law in Particular".

(Boggio et al. 2019[67]; Lang et al. 2019; EGE 2021, though they make no recommendation *per se*). Thus, the bans on creation of research embryos would need lifting for the benefits of human germline genome editing to be evaluated properly with a careful risk-assessment (Boggio et al. 2020). Similarly, though not in a human rights context, Kohn and his colleagues point out that "the regulatory framework for gene-editing procedures will necessarily focus on evaluating the potential medical benefit of the procedure vs. the potential for toxicity" (Kohn et al. 2016, 2557; see also EGE 2021).

The proportionality standard is a helpful tool for balancing with the interests of the public, but it burdens states with the obligation to justify limiting regulation. Some human rights instruments in biomedicine (e. g., the Oviedo Convention and the UDBHR) often attune the interests differently by establishing the principle of primacy of the human being, the downside being that enhancement or even eugenic practices may be supported. A possibly more suitable approach would be the precautionary principle which places the burden of proof and minimizing risks on the party introducing a new technology (Yotova 2020).

Though still "in its infancy", the so-called Responsible Research and Innovation approach seems especially suitable to guide self-regulation in the context of CRISPR.[68] It defines responsibility as "oriented towards the future", "collective and participative", "proactive" and in need of "concrete engagement by the relevant actors … with societal stakeholders" (Gorgoni 2018, 259). It combines other approaches including the pTA approach discussed above, for example. However, as with anything that requires broad consensus and is based on voluntary commitment, the standards tend to be vague or blurry at times, which can be a weakness and a strength to the same degree. Ultimately, explicitly embedding the Responsible Research and Innovation approach into the international human rights regime would give it a "constitutional identity" and simultaneously reap the benefits of its flexibility and its focus on inclusivity (Gorgoni 2018, 263). Encompassing this approach into the widely recognized legal regime of international human rights would provide stability and strengthen its validity, but given the fluid and inclusive nature of self-regulation, the risk of excessive rigidity can be mitigated.

67 See Boggio et al. 2019, 136–141 for an in-depth analysis on how different national legal frameworks currently fall short of the legality and proportionality requirements.

68 Although the Responsible Research and Innovation approach is discussed in the context of human enhancement, the same thoughts can be applied to therapeutic genome editing. The Responsible Research and Innovation approach differs from the well-established precautionary principle in that it focuses precaution more on the "cooperation between innovators and society", remedying the controversy around the political nature and lack of flexibility of the precautionary principle (Gorgoni 2018, 261; see also Hansson 2020).

3.3.3.2 Benefit Sharing, Non-Discrimination, and Solidarity

The principle of benefit sharing, codified in the ICESCR as well as the UNESCO declarations, calls to the parties to "recognize the right of everyone to enjoy the benefits of scientific progress and its applications" (art. 15 para. 1 ICESCR). States have the duty to, on one hand, use scientific knowledge to the benefit of all and, on the other hand, provide for non-discriminatory access policies (Boggio et al. 2020).[69] Art. 3 Oviedo Convention requires equitable access to healthcare and is an important application of the principle of non-discrimination (art. 11 Oviedo Convention; Council of Europe Steering Committee on Bioethics Preparatory Work Oviedo Convention 2000). Curtailing the testing of new technologies that could prevent suffering, be it by too restrictive a policy or funding constraints, would not conform to that standard (Boggio et al. 2019[70]).

Though heavily featured in the UNESCO declarations, the principle of solidarity is still not well defined. Solidarity in the sense of social justice can be derived from the ICESCR (see art. 2) and the principle of non-discrimination, but it can also be understood as the even distribution of risks and benefits (i. e., inclusion of vulnerable groups) or in the sense of "intergenerational equity" (i. e., respect for the rights of future progeny) (Boggio et al. 2020, 75–76; see also DRTFG). Alternatively, solidarity may also be interpreted more in the sense of benefit sharing, such that benefits should be shared as a public good (Mulvihill et al. 2017; Boggio et al. 2020).

To a certain extent, benefit sharing clashes with the private commercialization of genome editing technologies. Balancing public interests with private interests poses difficulties with any surfacing groundbreaking technology, with researchers finding themselves incentivized to direct their focus onto the commercial yields rather than the public good, which can be incompatible with solidarity (Carroll 2017; Mulvihill et al. 2017). Therefore, careful considerations on the privatization of the field and on equitable access to the benefits that germline genome editing can bring are required.

3.3.3.3 Respect for Human Dignity

As prominent as the principle of human dignity is in the UNESCO declarations, there is no consensus on what it entails (Boggio et al. 2020). How it applies in the context of human germline genome editing depends on the concept of human dignity one adopts, though no specific notion is distinguishable in international law.[71] Even if the notions of dignity presently advocated for may each guide the

69 See the language in the UDHGHR: "benefits from advances in biology, genetics and medicine, concerning the human genome, shall be made available to all".

70 Boggio et al. (2019, 141) argue that "legal systems must contemplate translational pathways to germline editing" and emphasize that applications of CRISPR to bring individuals to birth are premature

71 Be it a concept of *imago dei* according to Christian theology, which would prohibit any intervention in the creation of humans, or a concept closer to personal autonomy as di Pico della Mirandola

policymaking, further discussions about the scope of human dignity in the context of germline genome editing are essential.

3.3.3.4 Obligation to Respect and to Protect the Rights and Individual Freedoms of Others

Along with non-discrimination, the principle of respect and protection of the rights and individual freedoms of others is one of the most impactful principles of international law. It entails among others the rules protecting human subjects in research, e. g., risk and benefit assessment, research oversight (compatible with the freedom of research) as well as free and informed consent (Boggio et al. 2020).[72]

3.3.4 Interim Conclusion

As shown, policymakers can implement different legal instruments to regulate germline genome editing: Hard law (i. e., treaties or international agreements) and soft law (i. e., recommendations from non-governmental institutions and the scientific community itself). While hard law is burdened by the lengthy and difficult process of coming to a mutual understanding amongst sovereign states, once in place, it is legally binding and thus provides better penetrating power, which soft law lacks. However, the latter is more easily implemented precisely because it entails non-binding rules and allows for more inclusion and flexibility in regulating a rapidly evolving technology governed by fluctuating values.

An approach looking to mitigate the downsides of hard law and soft law, the human rights approach seeks to consolidate bioethics law (mostly soft law) and human rights law (hard law and well-established soft law). Considering that many of the existing soft law instruments refer to a number of principles established in international human rights law and often explicitly refer to them, the integration of bioethics law into the international human rights regime seems to be the favorable approach.

3.4 Continuous Monitoring, Enforcement, and Reevaluation

In order to preserve the values and legal standards established during the consensus-finding process and reflected in any proposed regulatory framework, as well as to keep irresponsible use of CRISPR at bay (Drabiak 2018; Boggio et al. 2019; EGE 2021[73]), the agreed upon policy needs to be enforceable (Bilir et al. 2021). Strong international collaboration and surveillance with effective reporting mechanisms and adequate sanctions will be imperative to ensuring compliance (Isasi and Knoppers 2015; NAS 2020; Townsend 2020; EGE 2021; Schaefer et al. 2021), especially given the cross-border work of scientists (Mulvihill et al. 2017) – this

and Kant have articulated, which would allow for arguments in favor of human germline genome editing fulfilling human dignity (see Boggio et al. 2020).

72 See above where the problem with the current conception of informed consent is discussed.

73 Focusing specifically on the oversight over commercialized "do-it-yourself" genome editing tools.

was brutally showcased by the incident involving the experiment of Jiankui He (NAS 2020; Schaefer et al. 2021).[74] Adequate monitoring and enforcement will in turn also uphold the integrity of the scientific community in the eyes of the public and foster trust (EGE 2021; Guttinger 2018 on the impact of bans on the trust in science) which is essential to maintain a regulatory framework based on soft law and, as shown above, self-regulation of the scientific community.

Needless to say, the topic of human germline genome editing is loaded with ethical controversies that need to be accommodated for – the "fluidity of the criteria and the evolution of extra-legal considerations" must be considered when designing the regulatory regime (Breczko 2021, 107). Continuous monitoring also allows for the public to be given more opportunities to continuously reassess the application of the technology to irreversibly engineer human DNA (CCNE 2019; Kaan et al. 2021 speaking of "adaptive consensus"; Schaefer et al. 2021). For human germline genome editing to be governed adequately, there must be enough flexibility to update the regulatory framework to new scientific findings (Halioua-Haubold et al. 2017 on gene therapy products in general), as well as shifting moral values of society and evolving legal conceptions (Kohn et al. 2016; Lang et al. 2019; EGE 2021; Kaan et al. 2021); a certain "regulatory learning curve" seems inevitable considering the speed with which technology advances in this day and age compared to how fast regulation can be imposed. Once more, the importance of a global oversight regime becomes clear: New findings can be disseminated quickly and among many, the risk assessment upon which the regulation rests can be revised, and the changes in ethical and legal considerations implemented accordingly (Kohn et al. 2016, 2558; Lang et al. 2019; EGE 2021).

While institutions required to monitor germline genome editing already exist, oversight regimes still require development (Evitt et al. 2015; Mulvihill et al. 2017 considering a similar approach to oversight over gene therapy already in place). What should most definitely be considered is a publicly accessible platform with an integrated registry for applications of CRISPR in germline genome editing contexts, coupled with an ethical approval requirement (EGE 2021). For this purpose, a platform for information sharing and inclusive debate over the data collected should be created,[75] or alternatively, the genome editing registry launched by the WHO could be further developed to fulfill this function (WHO 2021b).

3.5 Who Is Responsible?

A fundamental question to consider is: Who is to be responsible for providing the platform, guiding process for the debate on heritable human genome editing,

74 A number of scientists were allegedly aware of the experiment that Jiankui He was conducting and decided to neglect their obligation to report activities of that nature.

75 This should ideally be combined with the registry proposed by the WHO (chapter 3.3.2.2; see also EGE 2021).

and implementing regulation and oversight? Many authors are frustrated with the feeling that "nobody sets international law" (Eschner 2019).

Some contend that governments should be responsible for the governance of heritable genome editing, as they are backed by democratic legitimacy and because they are the actors bound by international law – international organizations and civil society, on the other hand, shall aid in implementing the policy (Boggio et al. 2020). The WHO, for instance, has already set up a registry for human genome editing, which could be adjusted to fit what the future regulatory framework governing heritable human genome editing intends to achieve at any given time (WHO 2021b). Another less coercive possibility (compared to traditional international lawmaking) would be delegating the regulatory power to a representative group of states (Yotova 2020).

Indeed, governments are the main subjects of traditional international law (Boggio et al. 2020). However, it will prove very difficult to have an international agreement negotiated by states without the involvement of actors who have already very extensively explored the questions surrounding heritable human genome editing, such as the UNESCO and WHO, or the interdisciplinary Global Observatory for Genome Editing comprised by experts from various fields (Jasanoff and Hurlbut 2018).[76] Basing the regulatory regime on the expertise that non-governmental institutions aggregate (be it in the field of gene editing itself or in the social sciences or law) is imperative, and thus these actors should play a central role in the process of regulating germline genome editing. It is true that, even though they bring a lot of proficiency in their respective fields, the WHO and UNESCO are not regulatory bodies and cannot enforce a given policy (WHO 2021b). Nevertheless, placing a large part of the responsibility for the process and substance of regulation, as well as oversight, in these expert agents would be most adequate given the speed of technological advancement in the genome editing field (Jasanoff and Hurlbut 2018; Yotova 2020; EGE 2021).[77] In any event, the regulatory body should be interdisciplinary such as to take into account various perspectives that come into play (Yotova 2020).[78]

76 Even if the WHO does not see itself fit for that task (see WHO 2021a, 5–7).

77 See also art. 24 UDHGHR in which the UNESCO has declared that the UNESCO IBC shall "contribute to the dissemination of the principles set out in this Declaration and to the further examination of issues raised by their applications and by the evolution of the technologies in question".

78 See also the section "Consolidating Different Consensuses: Participatory and Inclusive Debate" where it is explained that experts often fail to consider certain aspects that marginalized groups prioritize.

4 Conclusion

The emergence of the transformative technology named CRISPR, with its immeasurable potential for good and bad alike, has shaken the world of genetic engineering. Most controversially discussed is the advent of human germline genome editing. How can humankind reap the benefits of CRISPR while adequately safeguarding itself from the potential implications?

This question may elicit different responses from policymakers. The options are: Enacting a blanket ban, imposing a moratorium, more or less prohibitive regulation, or giving unregulated permission (Bosley et al. 2015). For the moment, both approaches at each end of the spectrum seem impossible (Evitt et al. 2015) and untenable from a human rights perspective (Boggio et al. 2019). Though maintaining the status quo of national regulation of CRISPR may be the garden path, such an approach will lead to more inefficiencies in the future (Tomlinson 2018 on the example of the U.S. "Coordinated Framework" system). To the contrary, a global regulatory regime seems indispensable to adequately deal with this heritable human genome editing.

However, first and foremost, inclusive dialogue should be focused on if and for what purposes CRISPR can and should be used to edit the human germline (Schleidgen et al. 2020; EGE 2021). Only with coming to a decision to the questions of "if" and "what for" can we move on to whether pre-clinical research is permissible (Andorno et al. 2020), especially given the uncertainties revolving around autonomy and informed consent, and to taking the steps to re-design the crucial legal concepts accordingly in order to preserve the interests of the research subjects. The pTA is a method that shows promise in providing a structure to contribute to the quality of the debate and its outcome (Weller et al. 2021). However, this approach leads to additional questions with regard to the discussion leaders, responsibility for the platform, and the conditions and requirements for a decision-making process.

In the interim, considering the novelty of the technology and the uncertainties around unforeseen consequences for future generations, the establishment of a moratorium limiting applications of CRISPR to induce heritable edits of human DNA appears to be a reasonable temporary solution. Such an approach is proposed by many (amongst others UNESCO IBC 2015; CCNE 2019; GEC 2019), but certainly not all (see Yotova 2020), while some authors consider a regulatory ban of heritable human genome editing to be unrealistic (e.g., Krekora-Zajac 2020). It is only when research involving human subjects has been deemed admissible and the conditions for it are met, i.e. the technology along with its effects have been explored and the necessary protections put in place under the inclusion and to the satisfaction of all relevant stakeholders, that possible clinical applications may

be seriously considered (Evitt et al. 2015, 26–29 for a detailed plan for the regulation of the concrete process of translating from research to clinical application).

To govern this process, policymakers may consider a range of approaches and employ different legal instruments (international agreements and international soft law) (WHO 2021a). However, focusing either on binding treaties or soft power only comes with significant drawbacks. Negotiating or renegotiating international agreements, though they are legally binding (which may deter states which are still undecided in their stance), involves a lengthy implementation process and lacks flexibility. Soft law prevails with its inclusiveness and plasticity but falls short on enforceability. Therefore, as argued in this paper, the human rights approach, i. e., the integration of bioethics law into the international human rights regime, could be a compromise that draws on the advantages on both soft and hard law. Constructing the regulatory framework with soft power instruments, but on the basis of already widely established and binding human rights and fundamental freedoms (especially the right to science and the rights of science), gives it the necessary flexibility and penetrating power.

In order to push forward such a suggested human rights-based approach to regulating genome editing, there is a pressing need to establish a platform and agencies responsible for continuous surveillance of human germline genome editing, enforcement of policies that may have been enacted, and collection of data. Furthermore, cooperation should be encouraged in order to continuously evaluate the risks and benefits of the technology according to the scientific findings. The Global Genome Editing Observatory, which has already been collecting a substantial amount of data on heritable human genome editing, would lend itself well for information gatherings. The same platform should also be used to conduct pTAs with key stakeholders (i. e., expert scientists from various disciplines, politicians, civil society including people affected by heritable human genome editing especially, etc.) and to disseminate the information across the globe so that remaining and newly emerging questions may be assessed and the regulatory framework (be it about the research or the prospective clinical application of CRISPR in germline engineering) continuously reevaluated against current ethical, societal, and legal backdrops (EGE 2021). This could be achieved by conducting pTAs on a local level to then escalate the conversation to a more global level, i. e. by gathering representatives of each group of stakeholders for further evaluation of the technology and the governance thereof. Enforcement of the given legal framework and oversight over compliance with it, however, will largely depend on the policy it entails. Forms of enforcement could range from delegation to national agencies tasked ensuring compliance to predominantly self-regulation of the scientific community, most prominently under the guidance of recommendations of international organizations such as the WHO or UNESCO.

It will be difficult to design an efficient global governance framework that will be complied with by all states – however, there is no time to spare. The big controversy of if, how, and for what purposes CRISPR should be applied to alter the human genome can hardly be decided once and for all, and many of the questions about the ethics of heritable human genome editing have been answered only in part, if at all. Thus, first and foremost, further in-depth debate involving all stakeholders is essential to embark on the journey to responsible use of CRISPR – to realizing its full potential.

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List of Abbreviations

CCNE	Comité Consultatif National d'Éthique pour les sciences de la vie et de la santé (National Consultative Ethics Committee for Health and Life Sciences)
CRISPR	clustered regularly interspaced short palindromic repeats
DNA	deoxyribonucleic acid
DRTFG	Declaration on the Responsibilities of the Present Towards Future Generations
ECHR	European Convention for the Protection of Human Rights and Fundamental Freedoms
EGE	European Group on Ethics in Science and New Technologies
EU	European Union
GEC	German Ethics Council
IBC	International Bioethics Committee
ICESCR	International Covenant on Economic, Social and Cultural Rights
IDHGD	International Declaration on Human Genetic Data
NAS	National Academies of Sciences
NCB	Nuffield Council on Bioethics
OECD	Organisation for Economic Co-operation and Development
RAIS	Research Association for Interdisciplinary Studies
RRI	Responsible Research and Innovation
UDBHR	Universal Declaration on Bioethics and Human Rights
UDHGHR	Universal Declaration on the Human Genome and Human Rights
UDHR	Universal Declaration of Human Rights
UN	United Nations
UNESCO	United Nations Educational, Scientific and Cultural Organization
U.S. / US	United States of America
WHO	World Health Organization

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