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Human Germline Editing

Legal Framework in Switzerland and Abroad*

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Abstract: This article looks into the regulation of human genome editing, particularly germline editing, in Switzerland and abroad. Following an overview of the Swiss legal framework, this article provides insights into regulations of other countries with a focus on embryo gene editing. After highlighting the fragmented character of current policies, the article discusses challenges and prospects in the regulation of human germline editing.

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I. Introduction

Genome editing technologies,[1] which enable targeted changes in an organism's DNA, are evolving rapidly.[2] Thanks to scientific advances and improved tools such as CRISPR/Cas9,[3] human genetic engineering has not only become possible but has also gained in safety, preciseness, and efficiency.[4] Moreover, the technology has become widely accessible: today, you can even order CRISPR kits on the internet through communities of biohackers.[5] Although these advances may be welcomed, significant concerns remain over potential misuse, particularly in human germline editing, or heritable genome editing.[6] Genome modification technologies indeed bear the promise of curing severe diseases but also raise fears of designer babies and unwanted repercussions for

1 The term *genome* editing is mostly used here, in comparison to *gene* editing, because the interventions made often change more than one gene, or even change DNA that is not in what is usually considered a gene. Henry T. Greely, CRISPR'd Babies: Human Germline Genome Editing in the 'He Jiankui Affair', in: Journal of Law and the Biosciences, 2019, 6(1), 111–183, 115.

2 Hongyi Li/Yang Yang/Weiqi Hong *et al.*, Applications of Genome Editing Technology in the Targeted Therapy of Human Diseases: Mechanisms, Advances and Prospects, in: Signal Transduction and Targeted Therapy, 2020, 5(1), 1–23, 1.

3 *CRISPR* stands for *clustered regularly interspaced palindromic repeats,* while *Cas9* is an RNA-programmable DNA endonuclease. Jennifer A. Doudna/Emmanuelle Charpentier, The New Frontier of Genome Engineering with CRISPR-Cas9, in: Science, 2014, 346(6213), 1258096.

4 National Academies of Sciences, Engineering, and Medicine, Statement by the Organizing Committee of the Second International Summit on Human Genome Editing, 28 November 2018, https://www.nationalacademies.org/news/2018/11/statement-by-the-organizing-committee-of-the-second-international-summit-on-human-genome-editing.

5 Annie Sneed, Mail-Order CRISPR Kits Allow Absolutely Anyone to Hack DNA, in: Scientific American, 2017, https://www.scientificamerican.com/article/mail-order-crispr-kits-allow-absolutely-anyone-to-hack-dna/.

6 For a definition of *germline editing,* also termed *heritable genome editing,* see subsection II.

future generations. In 2018, the first clinical application of human germline editing, the birth of twins whose genes had been edited as embryos, was reported by He Jiankui, a Chinese researcher. This gave rise to strong reactions worldwide and generally took the debate to another level.[7] However, even if interventions in the germline are mostly viewed as crossing a red line, an increasing number of voices is in favor of analyzing their potential ethical defensibility under certain circumstances. Against a background of changing perceptions of gene editing tools, the question arises whether a possible shift from *if* to *how* could take place,[8] as well as, if possible, where to then draw the line. The aim of this article is to give an overview of the current legal framework governing human genome editing, particularly germline editing, in Switzerland and in a comparative perspective. Firstly, this article provides some considerations on the advent of human genome editing. Secondly, it discusses the absence of a unified international legal framework in the field. Thirdly, this article examines the Swiss legal framework on human genome editing and provides insights into regulations of other countries, with a focus on embryo gene editing. After highlighting the fragmented character of current policies, the article discusses challenges and prospects in the regulation of human germline editing.

II. Advent of Human Genome Editing

Genome editing can be performed with various tools, and these have improved significantly in recent years. Although the discovery of CRISPR/Cas9 has marked the beginning of a new era in the field, the efficiency of other methods, such as base editing and prime editing, is currently being assessed to improve results and limit possible adverse, or *off-target,* mutations.[9]

Independent of the methods used, human genome editing is usually classified in two categories:[10]

- *Germline editing,* which is also referred to as *heritable genome editing,* involves a modification of the genetic material of the heritable genome. This usually presupposes interventions on germline cells, which are cells that may pass on their genetic material to the offspring, such as reproductive cells, also termed *gametes:* sperm cells and ova. The modification undertaken is therefore passed on to future generations and affects the offspring, not just the individual concerned.
- *Somatic genome editing,* which is also referred to as *therapeutic gene editing* or *somatic gene therapy,* involves a modification of the genetic material of somatic cells. These are all the cells of an organism except the germline cells and include, for instance, skin and blood cells. In contrast to germline editing, the modification is not passed down to future generations.[11]

Whereas somatic gene therapy is already being implemented to treat genetic diseases in clinical trials in many scientifically advanced countries, including Switzerland,[12] this is not the case for germline editing. The advent of the latter indeed raises additional ethical and social concerns, particularly over the safety of subsequent generations and the potential misuse for human enhancement.

III. Absence of a Unified International Legal Framework on Human Genome Editing

To date, there is no unified international legal framework in the field of human genome editing. Some soft law instruments are available, one of the most important being the 1997 UNESCO Universal Declaration on Human Genome and Human Rights.[13] Moreover, some binding legal instruments are available at the regional level. These include the Council of Europe's Oviedo Convention[14] as well as some Europe-

7 Shuang Liu, Legal Reflections on the Case of Genome-edited Babies, in: Global Health Research and Policy, 2020, 5(24), 1–3, 1.

8 Swiss National Advisory Commission on Biomedical Ethics NCE, Gene Editing an menschlichen Embryonen – Eine Auslegeordnung, Stellungnahme Nr. 25/2016, 2016, 4, https://www.nek-cne.admin.ch/inhalte/Themen/Stellungnahmen/NEK_Gene_editing_Papier_web_DEF.pdf.

9 See e.g. Janine Scholefield/Patrick T. Harrison, Prime Editing – An Update on the Field, in: Gene Therapy, 2021, 28, 396–401; and Elizabeth M. Porto/Alexis C. Komor/Ian M. Slaymaker/Gene W. Yeo, Base Editing: Advances and Therapeutic Opportunities, in: Nature Reviews Drug Discovery, 2020, 19(12), 839–859.

10 Mary Todd Bergman, Perspectives on Gene Editing, in: The Harvard Gazette, 9 January 2019, https://news.harvard.edu/gazette/story/2019/01/perspectives-on-gene-editing/.

11 Todd Bergman (footnote 10).

12 Alessandro Blasimme/Dorothée Caminiti/Effy Vayena, The Regulation of Human Germline Genome Modification in Switzerland, in: Andrea Boggio/Cesare P.R. Romano/Jessica Almqvist (eds), Human Germline Modification and the Right to Science: A Comparative Study of National Laws and Policies, Cambridge 2020, 409–438, 434; see also e.g. Robert Sanders, FDA Approves First Test of CRISPR to Correct Genetic Defect Causing Sickle Cell Disease, in: Berkeley News, 30 March 2021, https://news.berkeley.edu/2021/03/30/fda-approves-first-test-of-crispr-to-correct-genetic-defect-causing-sickle-cell-disease/.

13 Cesare P.R. Romano/Andrea Boggio/Jessica Almqvist, The Governance of Human (Germline) Genome Modification at the International and Transnational Level, in: Boggio/Romano/Almqvist (footnote 12), 22–80, 31.

14 Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine of the Council of Europe, ETS No. 164.

an Union (EU) directives and regulations.[15] The Oviedo Convention, which has been in force in Switzerland since 2008,[16] prohibits germline editing and provides that *"an intervention seeking to modify the human genome may only be undertaken for preventive, diagnostic or therapeutic purposes and only if its aim is not to introduce any modification in the genome of any descendants"* (Article 13). Although the Oviedo Convention is a legally binding instrument, its reach remains regional and it has only been ratified by a limited number of countries.[17] Against this background, it is no surprise that significant disparities in regulation, or its absence, exist between countries and regions. An increasingly common concern is therefore that a new form of reproductive travel or of *ethics dumping* could emerge. The latter refers to situations in which practices that would not be ethically accepted in some jurisdictions are undertaken in settings that do not forbid them.[18]

In response to this fragmented regulatory environment and in fear of potential misuse, various initiatives have emerged in recent years. For example, a World Health Organization (WHO) advisory committee was formed in 2018 with the aim of developing standards for the governance and oversight of human genetic engineering. In particular, this global and multidisciplinary advisory committee was tasked to *"examine the scientific, ethical, social and legal challenges associated with human genome editing (somatic, germline and heritable)."*[19] In 2019, the committee stated that *"it would be irresponsible at this time for anyone to proceed with clinical applications of human germline genome editing."*[20] In 2021, it published a framework for governance on human genome modification, along with recommendations on the subject.[21] These documents provide advice and recommendations on *"appropriate institutional, national, regional and global governance mechanisms for human genome editing."*[22] Concurrently with the WHO's efforts, a call for a global moratorium on all clinical uses of human germline editing was made in 2019 by a group of scientists,[23] including Nobel Prize winner Emmanuelle Charpentier, one of the researchers involved in the discovery of CRISPR/Cas9: *"until the technical, scientific, medical, societal, ethical and moral implications have been more thoroughly discussed and understood."*[24] Although these initiatives have contributed to greater attention and caution being paid to the topic, large gaps, inconsistencies, and grey areas remain in the various regulations.

IV. Swiss Legal Framework

Switzerland is characterized by a restrictive legal framework on human genome editing. Cloning and all interventions in the human germline are prohibited,[25] while somatic gene therapy is allowed under strict conditions.[26] Moreover, Switzerland's regulatory approach on assisted reproductive technologies is among the most restrictive ones in Europe.[27]

A. Relevant Sources, Principles, and Provisions

In addition to the few international instruments that are binding for Switzerland,[28] relevant sources on human genome editing include the Federal Constitution ("Fed. Cst.")[29] and federal laws such as the Reproductive Medicine Act ("RMA"),[30] the Stem Cell Re-

15 See e.g. the "European Clinical Trials Regulation," which prohibits clinical trials involving human germline editing (Article 90 of the Regulation (EU) No. 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC). Moreover, research activities intended to modify human germline cells are excluded from EU funding. Aurélie Mahalatchimy/Pin Lean Lau/Phoebe Li/Mark L. Flear, Framing and Legitimating EU Legal Regulation of Human Gene-Editing Technologies: Key Facets and Functions of An Imaginary, in: Journal of Law and the Biosciences, 2021, 8(2), lsaa080, 16.

16 Switzerland signed the Oviedo Convention on 7 May 1999 and ratified it on 24 July 2008. The convention entered into force in Switzerland on 1 November 2008. Council of Europe, Chart of Signatures and Ramifications of Treaty 164, https://www.coe.int/en/web/conventions/full-list/-/conventions/treaty/164/signatures.

17 For an overview of signatures and ratifications of the Oviedo Convention, see Council of Europe (footnote 16).

18 European Commission, Horizon 2020 Work Programme 2014–2015 – Science with and for Society – Revised, 2015, 35, https://ec.europa.eu/research/participants/data/ref/h2020/wp/2014_2015/main/h2020-wp1415-swfs_en.pdf.

19 WHO, Human Genome Editing: Recommendations, 12 July 2021, viii, https://www.who.int/publications/i/item/9789240030381.

20 WHO, Statement on Governance and Oversight of Human Genome Editing, 26 July 2019, https://www.who.int/news/item/26-07-2019-statement-on-governance-and-oversight-of-human-genome-editing.

21 WHO, Human Genome Editing: A Framework for Governance, 12 July 2021, https://www.who.int/publications/i/item/9789240030060; WHO (footnote 19).

22 WHO (footnote 21), vi.

23 Eric Lander/Françoise Baylis/Feng Zhang *et al.*, Adopt a Moratorium on Heritable Genome Editing, in: Nature, 2019, 567, 165–168, 165.

24 UN Development, Playing with Genes: The Good, the Bad and the Ugly, 2019, 1–6, 6, https://www.un.org/development/desa/dpad/wp-content/uploads/sites/45/publication/FTQ_May_2019.pdf.

25 Article 119, para. 2, letter a of the Federal Constitution of the Swiss Confederation of 18 April 1999, RS 101 ("Fed. Cst.").

26 Franziska Sprecher, Genom-Editierung an menschlichen Embryonen: Herausforderungen des Rechts, in: AJP, 2017, 1471–1485, 1475.

27 Andrea Büchler, Das Recht der Fortpflanzungsmedizin in der Schweiz, in: SJZ, 2019, 115, 375–383, 375; Sprecher (footnote 26), 1473.

28 For instance, the Oviedo Convention (see in particular Article 13).

29 Federal Constitution of the Swiss Confederation of 18 April 1999, RS 101 ("Fed. Cst."); see in particular Article 119 on reproductive medicine and gene technology involving human beings.

30 Federal Act on Medically Assisted Reproduction of 18 December 1998, RS 810.11 ("RMA").

search Act ("StRA"),[31] the Human Genetic Testing Act ("HGTA"),[32] the Transplantation Act,[33] and the Human Research Act ("HRA").[34] Moreover, various federal ordinances are applicable. These include the Reproductive Medicine Ordinance,[35] the Stem Cell Research Ordinance,[36] the Human Research Ordinance,[37] and the Clinical Trials Ordinance ("ClinO").[38] Finally, important nonbinding tools include opinions issued by the National Advisory Commission on Biomedical Ethics, in particular an opinion from 2019 on human embryo gene editing.[39]

Switzerland's restrictive regulatory approach to gene editing technologies is *inter alia* governed by the following principles: the protection against the misuse of reproductive medicine and gene technology[40] and the protection of human dignity, privacy, and the family.[41] The prevention of the misuse of surplus embryos and embryonic stem cells also plays an important role.[42]

In line with these principles, a precautionary approach has been adopted by the Swiss legislator.[43] Various genome editing practices are prohibited, including all interference in the human germline. The Federal Constitution also provides that cloning is prohibited[44] and that nonhuman reproductive and genetic material may neither be introduced into nor combined with human reproductive material.[45] Moreover, any kind of trade in human reproductive material and in products obtained from embryos is forbidden.[46] Finally, creating embryos for research purposes is also prohibited.[47]

B. Prohibitions of Interventions in the Human Germline

As outlined above, interventions in the human germline are constitutionally prohibited in Switzerland.[48] The RMA also provides for a criminal prohibition of modifications in the human germline.[49] An analogous ban is included in Article 13 of the Oviedo Convention, pursuant to which an intervention seeking to modify the human genome may not be undertaken to introduce *"any modification in the human genome of any descendants."*[50]

Even if the Swiss constitutional ban only mentions human reproductive cells and embryos, it covers all interventions in the human germline. The notion of human germline must be interpreted broadly[51] and encompasses fetuses,[52] embryos,[53] gonads,[54] and all germline cells.[55] The broad concept of germline cells[56] includes sperm cells and ova (including their

31 Federal Act on Research Involving Embryonic Stem Cells of 19 December 2003, RS 810.31 ("StRA").
32 Federal Act on Human Genetic Testing of 8 October 2004, RS 810.12 ("HGTA").
33 Federal Act on the Transplantation of Organs, Tissues and Cells of 8 October 2004, RS 810.21.
34 Federal Act on Research involving Human Beings of 30 September 2011, RS 810.30 ("HRA").
35 Reproductive Medicine Ordinance of 4 December 2000, RS 810.112.2.
36 Ordinance on Research Involving Embryonic Stem Cells of 2 February 2005, RS 810.311.
37 Ordinance on Human Research with the Exception of Clinical Trials of 20 September 2013, RS 810.301.
38 Ordinance on Clinical Trials in Human Research of 20 September 2013, RS 810.305 ("ClinO").
39 NCE (footnote 8).
40 Article 119, para. 1 Fed. Cst.
41 Article 119, para. 2 Fed. Cst.; Véronique Boillet, Commentary on Article 119, in: Vincent Martenet/Jacques Dubey (eds), 'Romand' Commentary on the Swiss Federal Constitution, Basel 2021, no. 21 *et seq.*
42 Article 1, para. 2 StRA.
43 Blasimme/Caminiti/Vayena (footnote 12), 428.
44 Article 119, para. 2, letter a Fed. Cst.
45 Article 119, para. 2, letter b Fed. Cst.
46 Article 119, para. 2, letter e Fed. Cst.
47 Article 119, para. 2, letter c Fed. Cst; Article 3, para. 1, letter a StRA. See also Article 18, para. 2 Oviedo Convention.
48 Article 119, para. 2, letter a Fed. Cst. At the time the ban was put in place, three main reasons underlying it were advanced. First, fundamental principles were invoked. According to these, germline interventions would not heal humans but alter their natural identity. Second, some invoked the *slippery slope* argument, saying that interventions initially limited to preventive or therapeutic purposes, which could be ethically defensible, could at some point lead to enhancement, which is not ethically admissible. Finally, some pragmatic and technical reasons were put forward, pursuant to which the prohibitions would only aim to protect against the lack of maturity of the technology and the incalculable risks. Swiss Federal Council, Botschaft über die Initiative "zum Schutz des Menschen vor Manipulationen in der Fortpflanzungstechnologie (Initiative für menschenwürdige Fortpflanzung, FMF)" und zu einem Bundesgesetz über die medizinisch unterstützte Fortpflanzung (Fortpflanzungsgesetz, FMedG) vom 26. Juni 1996, BBl 1996 III 205, 282.
49 Article 35, para. 1 RMA.
50 Bernhard Rütsche/Dario Picecchi, Allgemeiner Teil / IV. Teil: Kommentar zu Art. 119 BV / IV. Grundsätze (Abs. 2), in: Andrea Büchler/Bernhard Rütsche (eds), Fortpflanzungsmedizingesetz (FMedG), Bern 2020, no. 58 *et seq.*
51 Boillet (footnote 41), no. 19.
52 A foetus means the *"developing offspring from the end of organogenesis until birth"* (Article 2, letter j RMA).
53 An embryo means the *"developing offspring from the time of pronuclear fusion until the end of organogenesis"* (Article 2, letter i RMA).
54 Ovaries and testes.
55 Franziska Sprecher, Der Keimbahneingriff im schweizerischen Recht, in: Jochen Taupitz/Silvia Deuring (eds), Rechtliche Aspekte der Genom-Editierung an der menschlichen Keimbahn, Berlin/Heidelberg 2020, 273–361, 275 *et seq.*; Ruth Reusser/Rainer Schweizer, Commentary on Article 119, in: Bernhard Ehrenzeller/Benjamin Schindler/Rainer Schweizer/Klaus Vallender (eds), St. Gallen Commentary on the Swiss Federal Constitution, 3rd edn., Zurich 2014, no. 13 and the cited references.
56 Article 2, letters e and f, and Article 35, para. 1 RMA, and Article 3, para. 1, letter b StRA. The English translation of Article 3, para. 1, letter b StRA mentions *germ cells*, while referring to Article 35, para. 1 RMA, which refers to *germline cells*. This slight difference may be ignored by reference to the official versions of these laws, English not being an official language of the Swiss Confederation and the English translations being provided for information purposes only. The official German, French, and Italian versions of the articles mentioned refer to the same term, i. e. *Keimbahnzelle* (German), *cellules germinatives* (French), and *cellula della via germinale* (Italian).

precursor cells), impregnated ova[57] and embryonic cells whose genetic material can be passed on to offspring.[58] However, the definition of the human germline does not cover the placenta and the umbilical cord blood.[59]

The prohibition applies irrespective of the intervention's purpose, whether for therapy, research, or enhancement.[60] The interventions covered by the prohibition comprise *"all targeted changes that either introduce new genes into the genome or activate or deactivate existing genes."*[61] This includes mitochondrial replacement therapy:[62] the replacement of a woman's abnormal mitochondrial DNA with a donor's healthy one in the course of an *in vitro* fertilization (IVF).[63] Conversely, a variety of practices are excluded from or not covered by the prohibition. These include observational studies and observations in the context of pre-implantation genetic testing (PGT) and prenatal tests. In addition, unintentional mutations to the germline, for example due to chemotherapy, do not fall under the ban.[64] Similarly, indirect influence on the genome of the offspring, for instance by selecting an embryo following PGT, is not covered by the prohibition. Lastly, somatic genome editing is not included in the scope of the federal ban because it does not affect the germline.[65] Instead, this kind of genetic engineering is allowed with restrictions. In particular, clinical trials of somatic gene therapy are subject to special provisions.[66] *In vivo* and *ex vivo* gene therapies have to be approved by the Swiss Agency for Therapeutic Products (Swissmedic) or by the Swiss Federal Office of Public Health.[67] More generally, Article 13 of the Oviedo Convention requires a preventive, diagnostic, or therapeutic purpose for somatic gene therapy to be performed.[68]

The strict constitutional ban underscores the fact that human germline editing can be performed under no circumstances in Switzerland. This applies not only to research, but also to clinical applications; in this context, that means when human genome editing is used on patients in a clinical setting.[69] Yet sources and interpretations of the ban's scope vary depending on what is gene-edited. To illustrate this, the examples of genome editing in gametes, embryos, and embryonic stem cells, both in research and in clinical applications, are outlined below from a Swiss legal perspective.

1. Gametes

As discussed above, the Swiss Federal Constitution strictly and explicitly prohibits interference with the genetic material of human reproductive cells, also termed gametes:[70] sperm cells and ova.[71] The RMA and the StRA also prohibit the gene editing of gametes.[72] As regards artificial gametes, the source of which could be human embryonic stem cells, their production and handling are not explicitly addressed by Swiss law. However, the broad wording of the human germline editing ban supports the assumption that artificial gametes are also covered by the ban.[73]

The prohibition applies to all stages of research on gametes involving gene editing.[74] Further, the importation of genetically modified germline cells, including gametes, is not allowed within the StRA.[75] In line with the prohibition on editing the genes of gametes, a pregnancy with genetically modified gametes, which would be a clinical application of gene editing of reproductive cells, is also prohibited by Swiss law.[76] Finally, Swiss law does not forbid the conduct of research on gametes if no genome editing is involved.

2. Embryos

Swiss law defines the human embryo as the *"developing offspring from the time of pronuclear fusion until*

57 An impregnated ovum means the *"fertilized ovum before pronuclear fusion"* (Article 2, para. h RMA).
58 Article 2, letters e and f RMA; Rütsche/Picecchi (footnote 50), no. 58 *et seq;* Sprecher (footnote 26), 1474; Reusser/Schweizer (footnote 55), no. 23.
59 Reusser/Schweizer (footnote 55), no. 12; Brigitte Tag, Article 35 Eingriffe in die Keimbahn, in: Büchler/Rütsche (footnote 50), 664–668, 666, no. 3.
60 Sprecher (footnote 55), 286; Swiss Federal Council (footnote 48), 283.
61 Tag (footnote 59), no. 5. Authors' translation.
62 Rütsche/Picecchi (footnote 50), no. 60. On the topic, see also Andrea Büchler/Karène Parizer, Mitochondrial Donation – Birth of a Policy, in: Bioethica Forum, 2017, 10(1), 15–23.
63 Nishtha Saxena/Nancy Taneja/Prakriti Shome/Shalini Mani, Mitochondrial Donation: A Boon or Curse for the Treatment of Incurable Mitochondrial Diseases, in: Journal of Human Reproductive Sciences, 2018, 11(1), 3–9, 5.
64 Article 35, para. 3 RMA.
65 Sprecher (footnote 55), 277; Rütsche/Picecchi (footnote 50), no. 59 *et seq.;* Büchler (footnote 27), 1475.
66 See Article 22, para. 4, and Article 35 CliO. See also Article 19, para. 1, and Articles 25 and 37 of the Federal Ordinance on Transplantations.
67 Swiss Expert Committee for Biosafety SECB, Gene Therapy, https://www.efbs.admin.ch/en/topics/gene-therapy.
68 Benedikt van Spyk, Das Recht auf Selbstbestimmung in der Humanforschung, Zurich/St. Gallen 2011, 76.
69 Andrea Boggio/Cesare P.R. Romano/Jessica Almqvist, Toward a Human Rights Framework for the Regulation of Human Germline Genome Modification, in: Boggio/Romano/Almqvist (footnote 12), 585–617, 592.
70 Article 2, letter e RMA.
71 Article 119, para. 2, letter a Fed. Cst.
72 Article 35, para. 1 RMA and Article 3, para. 1, letter b StRA.
73 Sprecher (footnote 55), 289.
74 Blasimme/Caminiti/Vayena (footnote 12), 431 and 435.
75 Article 3, para. 1, letter e StRA.
76 Blasimme/Caminiti/Vayena (footnote 12), 436.

the end of organogenesis."[77][78] As in the case of gametes, the Swiss Federal Constitution contains a strict prohibition on interfering with the genetic material of human embryos.[79] The explicit prohibition on embryo gene editing applies in the contexts of research activities[80] and reproduction. In other words, a pregnancy with genetically modified embryos is strictly prohibited in Switzerland.[81]

Finally, the regulation regarding the conduct of general research on embryos but not involving genome editing is inconsistent. While research on *in vitro* embryos is not permitted,[82] research on *in vivo* embryos[83] and embryos stemming from abortions and stillbirths is explicitly allowed under restrictive conditions.[84] Creating embryos for research purposes is prohibited,[85] as is importing or exporting such research embryos or *surplus embryos:* embryos produced in the course of IVF procedures that cannot be used to establish a pregnancy and therefore have no prospect of survival[86].[87] However, embryos can be created *in vitro,* but only for use in assisted reproductive procedures.[88] Furthermore, surplus embryos may be used for the sole purpose of deriving embryonic stem cells, under restrictive conditions.[89] Such embryos may be used only up to the seventh day of their development.[90] While research on surplus embryos is prohibited under Swiss law,[91] research on embryonic stem cells derived from such surplus embryos is allowed. The prohibition of research on *in vitro* embryos, while allowing research on embryonic stem cells, can be seen as inconsistent, as in both cases the embryos end up being destroyed.[92] This inconsistency is likely linked to the unclear status of the embryo under Swiss law. Under the latter, an embryo does not benefit from any protection deriving from the status of *living being* until birth. However, it benefits from a certain limited protection.[93]

3. The Case of Embryonic Stem Cells

Under Swiss law, a human embryonic stem cell is defined as a cell from an IVF embryo *"with the ability to differentiate into the various cell types, but not to develop into a human being, and the cell line derived therefrom."*[94] Embryonic stem cells must be differentiated from embryonic cells *"whose genetic material can be passed on to offspring."*[95] As mentioned above, the derivation of human embryonic stem cells from surplus embryos is allowed under Swiss law.[96] However, such derivation is no longer permitted after the seventh day of the development of the surplus embryos.[97] In line with the constitutional ban on embryo germline modification, Swiss law prohibits the derivation of stem cells from an embryo that has undergone germline modifications.[98]

While research on human embryonic stem cells is permitted under Swiss law,[99] rigid conditions apply.[100] Interestingly, the genome editing of such cells for research purposes may seem, at least at first

77 The *organogenesis* refers to the moment when organ development is completed. This is the case at around the end of the eighth or ninth week of pregnancy. Swiss Federal Council (footnote 48), 247; Swiss Federal Council, Message sur la loi relative à la recherche sur l'être humain du 21 octobre 2009, FF 2009 7259, 7330.

78 Article 2, letter i RMA (Article 2, letter a StRA contains a similar definition). In this definition, Swiss law refers to an unclear concept to distinguish an *impregnated ovum* (Article 2, para. 2, letter h RMA) from an *embryo:* the concept of *pronuclear fusion*. This is defined by doctrine as the moment at which the male and female's genomes are inseparably physically unified. However, this term is not precise and is rather a legal fiction, as developmental biology provides no sufficient basis by which to distinguish an embryo from an impregnated ovum. Moreover, there are no convincing ethical grounds underlying the distinction between impregnated ova and embryos. The Swiss legal definition of embryo is therefore based on pragmatic, political considerations. Bernhard Rütsche, Article 2, in: Büchler/Rütsche (footnote 50), no. 30; Bernhard Rütsche, Rechte von Ungeborenen auf Leben und Integrität: Die Verfassung zwischen Ethik und Rechtspraxis, Zurich/St. Gallen 2009, 508 *et seq.;* BGE 119 Ia 460, E. 11c.

79 Article 119, para. 2, letter a Fed. Cst.

80 Blasimme/Caminiti/Vayena (footnote 12), 429.

81 Article 35, para. 2 RMA; Blasimme/Caminiti/Vayena (footnote 12), 437.

82 Swiss Federal Council (footnote 77), 7278; Valérie Savioz-Viaccoz, L'embryon in vitro: émergence d'un nouvel objet de droit, Qualification juridique et contrats, Zurich/Basel/Geneva 2021, 55; NCE (footnote 8), 4.

83 *In vivo* embryos are embryos in the womb (Matthias Till Bürgin, Commentary on Article 25, in: Berhard Rütsche (ed), Humanforschungsgesetz (HFG), Bundesgesetz vom 30. September 2011 über die Forschung am Menschen, Bern 2015, no. 2).

84 Sprecher (footnote 26), 1478. *In vivo* embryos can be the subject of research under certain conditions, only if such research serves a disease-related purpose. (Article 25 HRA *a contrario;* Bürgin (footnote 83), no. 1). Embryos stemming from abortions and stillbirths may also be the subject of research under restrictive conditions, provided that they have been declared dead (Articles 39 and 40 HRA).

85 Article 3, para. 1 lit. a StRA and Article 29 para. 1 RMA.

86 Article 2 lit. b StRA.

87 Article 3 para. 1 lit. e and para. 2 lit. b StRA.

88 Article 29 para. 1 RMA; art. 3 para. 1 lit. a StRA. Moreover, the genetic material of these embryos may be analyzed under restrictive conditions, for example as part of PGT or prenatal tests (Articles 5a and 5b RMA; Article 11 HGTA). However, the genetic testing of such embryos for nonmedical reasons is prohibited (Article 11 HGTA; Blasimme/Caminiti/Vayena (footnote 12), 429).

89 Article 1, para. 1 and Article 3, para. 2, letter a *a contrario* StRA.

90 Article 3, para. 2, letter c *a contrario* StRA.

91 Article 3, para. 2, letter a *a contrario* StRA.

92 NCE (footnote 8), 4; Sprecher (footnote 26), 1474.

93 Andrea Büchler/Margot Michel, Medizin – Mensch – Recht, Eine Einführung in das Medizinrecht der Schweiz, 2nd ed., Zurich/Basel/Geneva 2020, 21 *et seq.*

94 Article 2, letter c StRA.

95 Article 2, letter f RMA.

96 Article 1, para. 1 StRA.

97 Article 3, para. 2, letter c StRA.

98 Article 3, para. 1, letter b StRA.

99 Article 1, para. 1 and Article 3, para. 2, letter a StRA.

100 See Articles 11 *et seq.* StRA, in particular the mandatory approval for research project (Article 11), the scientific and ethical requirements for research projects (Article 12), and the duties of the project manager (Article 13).

glance, to be allowed.[101] In 2003, the Swiss Federal Council even held that *"it is not forbidden to modify the genome of embryonic stem cells because such a modification could not be genetically transmitted."*[102] Yet such a modified cell may only be studied *in vitro* and cannot be inserted into an embryo or otherwise used to give rise to an embryo.[103] Against this background, many authors are rightly of the view that embryonic stem cells are covered by the federal ban on human germline editing despite their inability to develop into a human being.[104] This is in line with the *ratio legis* of the ban with respect to both research and clinical applications.

Finally, it is also clear that clinical applications of gene-edited embryonic stem cells are excluded. Given the definition of embryonic stem cells, which do not have the ability *"to develop into a human being,"*[105] a pregnancy with such embryonic stem cells would not be possible in any case.

In conclusion, the prohibition of interference in the human germline must be interpreted broadly, in line with Switzerland's cautious and restrictive approach.

V. Insights into Regulations on Embryo Genome Editing in Other Countries

While Switzerland's legal framework on gene editing on humans is largely restrictive, this is not the case everywhere. To illustrate the large differences in regulation worldwide, the present section provides some insights into regulations on human germline editing in other countries, by focusing on the case of the embryo.

A. Research

Regulatory regimes governing embryo genome editing in research vary widely. First, some jurisdictions allow it under certain circumstances. Research indeed seems to be incorporating the use of gene editing technologies in embryos in countries with less restrictive regulations than Switzerland. This is particularly the case in the jurisdictions that allow the creation of research embryos. These are embryos that are intended to be used only for research, to the exclusion of reproductive purposes.[106] Among the countries allowing embryo gene editing in research are several EU countries such as Belgium, Sweden, and Greece;[107] several countries in Asia, albeit often through nonbinding guidelines;[108] and other countries such as the United Kingdom (UK).[109] The UK indeed allows targeted genetic modifications of surplus embryos at an early stage of development.[110]

Second, many countries prohibit research involving embryo genome editing. This is the case in several EU countries such as Austria, Germany,[111] and Poland, and in other jurisdictions such as Brazil and Canada.[112]

Finally, such research is still unregulated in many countries, for example Argentina, Russia, and the United States of America at federal level.[113]

Overall, the regulatory regimes differ significantly, even within the EU, and are sometimes ambiguous. This reflects varying ethical perspectives on this issue, particularly with respect to the moral status of the embryo.

B. Clinical Applications

To our knowledge, no jurisdiction explicitly permits clinical applications of embryo genome modification: gene editing of embryos for reproduction. The regulatory landscape is rather restrictive even if, sometimes, opinions vary on the interpretations of specific legislations.[114]

First, several jurisdictions do not clearly prohibit clinical applications of embryo genome editing or prohibit them with exceptions. This may leave the door open to germline editing being used in a clinical context, even though such interpretations have not yet been tested in court.[115] Surprisingly, Belgium, which is not a party to the Oviedo Convention, does not prohibit germline editing in embryos for therapeutic purposes, although this rather constitutes a legal grey area. In addition, any implementation would most likely be impossible in practice,

101 Swiss Federal Council, Botschaft zum Bundesgesetz über die Forschung an überzähligen Embryonen und embryonalen Stammzellen (Embryonenforschungsgesetz, EFG), BBl 2003 1163, 1243; Sprecher (footnote 55), 318. Blasimme/Caminiti/Vayena (footnote 12), 430–431.

102 Swiss Federal Council (footnote 101), 1243. Authors' translation.

103 Blasimme/Caminiti/Vayena (footnote 12), 431.

104 Sprecher (footnote 55), 318; Reusser/Schweizer (footnote 55), no. 23.

105 Article 2, letter c StRA.

106 Boggio/Romano/Almqvist (footnote 69), 587–588.

107 However, restrictions and sometimes strict conditions are usually applicable. Silvia Deuring, Vergleich der nationalen Regelungen, in: Taupitz/Deuring (footnote 55), 537–569, 538 *et seq.*

108 E.g. China, South Korea, and Singapore. Boggio/Romano/Almqvist (footnote 69), 587–588.

109 Heidi Ledford, The Landscape for Human Genome Editing, in: Nature, 2015, 526(7573), 310–311, 311.

110 NCE (footnote 8), p. 1.

111 Germany, which has a strict regulation on the use of embryos in assisted reproduction, limits research on human embryos. Violations can even result in criminal charges. Ledford (footnote 109), 310; Silvia Deuring, Keimbahninterventionen im Bereich der Forschung in vitro sowie mit Auswirkung auf geborene Menschen – Überblick über die nationalen Regelungen, in: Taupitz/Deuring (footnote 55), 485–535, 490 *et seq.*

112 Deuring (footnote 111), 532–533.

113 However, federal funding for such research is prohibited at federal level. Ledford (footnote 109), 310; Deuring (footnote 107), 542.

114 See also Françoise Baylis/Marcy Darnovsky/Katie Hasson/Timothy M. Krahn, Human Germline and Heritable Genome Editing: The Global Policy Landscape. In: The CRISPR Journal, 2020, 3(5), 365–377, 374.

115 Boggio/Romano/Almqvist (footnote 69), 592–593.

for the approval of an ethics committee would be needed, and this would likely not be given in light of current risks.[116] Curiously and counterintuitively, some scholars consider that the Italian legal framework leaves room for such clinical applications, because Italy, which signed but never ratified the Oviedo Convention, has no clear prohibition. However, doubts remain about the concrete possibility of allowing such clinical applications.[117] Moreover, clinical trials resulting in modifications to the human germline may not be carried out under EU law,[118] which makes the prospect of corresponding clinical applications even more remote. Another country worthy of mention is Israel, where embryo gene editing for reproduction is prohibited in principle. However, permission can be given by the Health Minister as long as the intervention does not violate human dignity and may have therapeutic benefit.[119] Finally, mitochondrial replacement therapy is allowed in the UK,[120] but it is not viewed as being germline editing there.[121]

Second and as outlined above, most countries explicitly prohibit embryo gene editing for reproduction. This is the case for most EU countries;[122] some Asian countries, albeit sometimes merely through non-binding guidelines;[123] and many other countries, which include Australia and Brazil. In these countries where clinical use is banned, research is sometimes permitted as long as it meets certain restrictions and as long as no live birth is generated.[124]

Finally, and similarly to what applies to research activities, clinical applications of embryo gene editing remain unregulated in many jurisdictions. This is typically the case in Argentina, despite the fact that reproductive cloning is explicitly prohibited there.[125] Russia should also be mentioned, even though regulations addressing the issue are currently under development.[126] A similar legal limbo exists in the United States of America. However, a pregnancy with a genetically modified embryo remains factually infeasible. Although no federal law expressly prohibits clinics from providing germline editing services, federal law prohibits the Food and Drug Administration (FDA) from accepting applications to begin clinical research. This also means that no clinical applications can be offered to patients.[127]

In sum, although legal frameworks vary and certain legal uncertainties remain to be addressed, most jurisdictions have adopted a restrictive stance against clinical applications of embryo genome editing.

C. Key Factors

In addition to whether or not embryo genome editing is allowed or regulated, some key factors play a fundamental role in practice, both to research and to clinical applications. First, a possible ban may be binding or not. Further, criminal provisions may or may not apply in cases of noncompliance with the law. Both factors can have practical impacts. In addition, what constitutes an embryo varies across countries as there is no consensus on the definition.[128] As a consequence, some regulations may not be as restrictive as they would first seem, or the opposite, depending on the definition used. Another important factor for research is whether or not research embryos can be created.[129] More generally, conditions of research vary between countries. In principle, the informed consent of the persons whose gametes were

116 Institut Européen de Bioéthique, La recherche sur les embryons humains en Belgique, 2019, 18–19, https://www.ieb-eib.org/docs/pdf/2019-02/doc-1554801302-19.pdf; Chambre des représentants de Belgique, 3e session de la 54e législature – Questions et réponses écrites, 2016, 219–220, https://www.lachambre.be/QRVA/pdf/54/54K0081.pdf; Institut Européen de Bioéthique, "Bébés-OGM": le Conseil de l'Europe réitère son opposition ferme, 5 December 2018, https://www.ieb-eib.org/fr/actualite/recherche-biomedicale/recherche-sur-les-embryons/bebes-ogm-le-conseil-de-l-europe-reitere-son-opposition-ferme-1530.html; Deuring (footnote 111), 514 *et seq.*; Deuring (footnote 107), 555 *et seq.*; Boggio/Romano/Almqvist (footnote 69), 592–593.

117 Ludovica Poli, The Regulation of Human Germline Genome Modification in Italy, in: Boggio/Romano/Almqvist (footnote 12), 335–357, 355 *et seq.*

118 Article 90 European Clinical Trials Regulation. Clinical trials using human germline modification are also explicitly prohibited by Italian law (see Article 6 Legislative Decree No. 211 of June 24, 2003), in accordance with EU law.

119 Vardit Ravitsky/Gali Ben-Or, The Regulation of Human Germline Genome Modification in Israel, in: Boggio/Romano/Almqvist (footnote 12), 568–582, 576; Boggio/Romano/Almqvist (footnote 69), 593; Global Gene Editing Regulation Tracker, Israel Germline/Embryonic, https://crispr-gene-editing-regs-tracker.geneticliteracyproject.org/israel-germline-embryonic/.

120 Human Fertilisation & Embryology Authority, Mitochondrial Donation Treatment, https://www.hfea.gov.uk/treatments/embryo-testing-and-treatments-for-disease/mitochondrial-donation-treatment/.

121 James Lawford Davies, The Regulation of Human Germline Genome Modification in the United Kingdom, in: Boggio/Romano/Almqvist (footnote 12), 217–240, 232.

122 E.g. in Germany, the Netherlands, Spain, and Sweden. Boggio/Romano/Almqvist (footnote 69), 592.

123 E.g. in China, India, and Japan. Ledford (footnote 109), p. 310; Boggio/Romano/Almqvist (footnote 69), 592.

124 Ledford (footnote 109), 310 *et seq.*

125 Ledford (footnote 109), 310; Global Gene Editing Regulation Tracker, Argentina Germline/Embryonic, https://crispr-gene-editing-regs-tracker.geneticliteracyproject.org/argentina-germline-embryonic/.

126 Deuring (footnote 107), 556; Global Gene Editing Regulation Tracker, Russia Germline/Embryonic, https://crispr-gene-editing-regs-tracker.geneticliteracyproject.org/russia-germline-embryonic/.

127 Deuring (footnote 111), 534.

128 Iñigo de Miguel Beriain, What is a Human Embryo? A New Piece in the Bioethics Puzzle, in: Croatian Medical Journal, 2014, 55(6), 669–671, 669.

129 The creation of embryos for research purposes is allowed in several EU countries (e.g. Belgium, Portugal, and Spain), as well as in China, Taiwan, South Korea, Singapore, and the UK, among others. Deuring (footnote 107), 538.

used is required.[130] Most jurisdictions have also adopted in some way the *14-day rule,* which prohibits experimenting on embryos 14 days after fertilization.[131] Finally, both a therapeutic purpose and the authorization of an ethics committee are usually required to proceed with the interventions discussed.[132] In sum, regulations in the field prove to be fragmented. In addition, even where particular policies may seem similar, the outcomes and practices can differ greatly, leaving room for uncertainties.

VI. Challenges and Prospects in the Regulation of Human Germline Editing

Today, many voices question the legitimacy of certain human genome editing bans. In particular, pressure is mounting to explore heritable genetic engineering for therapeutic purposes. This is especially due to advances that have rendered the newest gene editing technologies, including CRISPR/Cas9, safer and more precise.[133] Along with an increasing acceptance of germline editing,[134] some even write about a possible trend towards liberalization.[135] However, amidst a diversified legal landscape, major challenges remain. Further, a variety of questions, including important ethical issues, need to be addressed before paving the legal way for some forms of genome editing, in particular clinical applications of germline editing, both in Switzerland and in other countries. These challenges include some difficult delimitations. For instance, the legal way to use gene editing technologies is usually to serve therapeutic purposes and to cure diseases. The varying and sometimes unclear notion of therapy is thus essential. Yet it is often difficult to distinguish this notion from prevention or enhancement.[136] Another difficult delimitation is that between health and disease: how do we define the latter? In essence, this makes us question the concept of normality and the acceptable extent to which we can influence future generations using these powerful technologies. Another open issue in this field is the added value of gene editing in comparison with PGT. PGT involves genetic screening of embryos prior to the selection and implantation of one or more of them in the womb. Could the selection step involved in PGT be avoided and replaced by the gene editing of embryos? If so, is this desirable?[137] In general, human germline editing raises many other questions, such as the balance between the prevention of misuse versus scientific freedom and potential beneficial uses.[138] Other strong concerns must also be considered: of fairness, social justice, and nondiscrimination, among others. Amidst these challenges, it seems crucial that the wider public play some role in the debate on the permissibility and conditions of human germline editing, though such a role remains to be defined. The promotion of public confidence as well as public education is also of paramount importance, as fears and potential misrepresentations must be dealt with.[139]

Against this background, it is imperative that international cooperation involving all stakeholders address these challenges. Further, a global approach to regulation is needed. This is especially relevant amidst fears of a possible new form of reproductive travel if certain jurisdictions opt for a liberalization of their framework on gene editing in reproduction. Common definitions and clear guidelines with a broad reach must urgently be adopted while avoiding the hurdles of navigating the heterogeneous regulations across borders. Various approaches and combinations of these are possible: through soft law,[140] a human rights framework, or hard law; and each approach has its own drawbacks. For instance, soft law instruments such as those adopted by the WHO last year[141] can be adopted quickly and bear strong promises while remaining flexible. Yet such approaches have limited reach because they are not binding and may lack democratic legitimacy. An approach based on international human rights law also has the typical drawbacks and advantages linked to human rights standards.[142] In hard law, binding treaties are difficult and take time to negotiate. They also remain less flexible after their adoption. However, they usually provide greater accountability.

130 Deuring (footnote 107), 542.
131 However, the International Society for Stem Cell Research recently removed the 14-day rule from its Guidelines for Stem Cell Research and Clinical Translation. Robin Lovell-Badge/Eric Anthony/Roger A Barker *et al.*, ISSCR Guidelines for Stem Cell Research and Clinical Translation: The 2021 Update, in: Stem Cell Reports, 2021, 16(6), 1398–1408, 1398, https://www.cell.com/stem-cell-reports/fulltext/S2213-6711(21)00263-0.
132 See e.g. Deuring (footnote 107), 539–541.
133 Bijan Fateh-Moghadam, Genome Editing als strafrechtliches Grundlagenproblem, in: Medstra, 2017, 3, 146–156, 146.
134 NCE (footnote 8), 4; Blasimme/Caminiti/Vayena (footnote 12), 437.
135 Sprecher (footnote 55), 325.
136 On setting boundaries between therapy and enhancement, see: Judit Sándor, Genome Editing: Learning from Its Past and Envisioning Its Future, in: European Journal of Health Law, 2022, 1–18, 15 *et seq.*
137 NCE (footnote 8), 2.
138 Blasimme/Caminiti/Vayena (footnote 12), 412.
139 On the public opinion on CRISPR/Cas9 as derived from tweets, see: Martin Müller/Manuel Schneider/Marcel Salathé/Effy Vayena, Combining Crowdsourcing and Deep Learning to Assess Public Opinion on CRISPR-Cas9, in: bioRxiv, 2019, 802454.
140 As an example of soft law instruments, see: WHO (footnote 19) and WHO (footnote 21).
141 See: WHO (footnote 19) and WHO (footnote 21).
142 On international human rights law to regulate human germline editing, see: Boggio/ Romano/ Almqvist (footnote 69), 585–617.

VII. Conclusion

Genetic engineering tools are evolving rapidly. With such advances come new possibilities and prospects for their use on humans, particularly for therapeutic purposes. While these developments may be welcomed, significant concerns remain over potential misuse, in particular with respect to germline editing. Clinical applications of this technique are indeed largely condemned both by the scientific community and by regulators. Yet perceptions are changing, and some call for a renewed assessment of how we tackle germline editing regulation. While the Swiss legal framework on human genome editing is largely restrictive and germline editing is strictly prohibited, this is not the case everywhere. Without a unified international legal framework, policies worldwide vary widely, as is the case with embryo gene editing. This applies to both research activities and clinical applications, even though the latter face stronger restrictions. Amidst such a regulatory landscape and an increasing acceptance of germline editing, major challenges and a variety of questions remain, including important ethical issues. These should be addressed before liberalizing some forms of human genome editing, in particular germline editing for reproduction.