6-2021

The Regulation of Human Germline Genome Modification (HGGM) at the National Level: A Call for Comprehensive Legal Reform

Andrea Boggio
Bryant University, aboggio@bryant.edu

Cesare P.R. Romano
Loyola Law School Los Angeles

Jessica Almqvist
Lund University

Loyola of Los Angeles International and Comparative Law Review

Volume 43 | Number 3 Article 3

2021

The Regulation of Human Germline Genome Modification (HGGM) at the National Level: A Call for Comprehensive Legal Reform

Andrea Boggio

Cesare P.R. Romano

Jessica Almqvist

The Regulation of Human Germline Genome Modification (HGGM) at the National Level: A Call for Comprehensive Legal Reform

BY ANDREA BOGGIO, CESARE P.R. ROMANO, AND JESSICA ALMQVIST*

INTRODUCTION

The regulation of human germline genome modification (HGGM) had already been debated for at least a decade when Chinese doctor He Jianku dazed the world in December 2018 after announcing the birth of twins who had been genetically modified at the embryonic stage. However, He Jianku's announcement turned the question from a theoretical problem into an actual one, forcing international and national decision makers to pay more attention to the regulation of HGGM both at the national and international levels. Some states regulate HGGM using legal instruments that date back to the 1990s or early mid-2000s, long before the advent of CRISPR made genetic editing considerably easier and cheaper.

It is necessary to better understand how HGGM is regulated at the national level. Scientists need this understanding if they are to act responsibly and be confident that they are on the right side of the law. Additionally, better national regulatory frameworks are also necessary to achieve the creation of an international regulatory regime. As the World Health Organization's Expert Advisory Committee on Developing Global Standards for Governance and Oversight of Human Genome Editing points out, national regulations are essential in the development of international and transnational governance of human genome editing because

* Andrea Boggio is Professor of Legal Studies, Department of History and Social Sciences, Fellow of Center for Health and Behavioral Sciences, Bryant University. Cesare P.R. Romano is Professor of Law, W. Joseph Ford Fellow, and Director of the International Human Rights Center, Loyola Law School, Los Angeles. Jessica Almqvist is Professor of International Law and Human Rights, Law Faculty, Lund University. The authors wish to thank the editors of the Journal, particularly its Editor-in-Chief, Saphya Council, and the scholars that have contributed to the edited volume titled "Human Germline Modification and the Right to Science: A Comparative Study of National Laws and Policies" (CUP 2020), which work has provided the empirical foundations of this paper.

governance is comprised of "a web of separate initiatives," including initiatives led by national lawmakers and regulators.[1]

During the past three years, we carried out a comparative study of national regulatory frameworks of HGGM, and published the results in a volume entitled "Human Germline Modification and the Right to Science: A Comparative Study of National Laws and Policies."[2] We invited experts in 18 states around the world to write essays discussing at great length how HGGM is regulated in their state.[3] We also included an essay discussing the regulation of HGGM in Europe (European Union and Council of Europe), as well as on the global level. We published extensive, critical analyses of these regulatory frameworks in light of the pre-existing international human rights obligations of individual states. In particular, we focused on the so-called "right to science" (or, less succinctly, the right to benefit from progress in science and technology), as well as the rights of scientists and those that protect scientific research (the so-called "rights of science"). At the global level, these rights are codified in the Universal Declaration of Human Rights[4] and the International Covenant on Economic, Social and Cultural Rights,[5] and at the regional level, they are set out in numerous legal instruments.[6] We will not repeat these analyses here. Instead, this article further elaborates on the data presented in the essays in the book to facilitate comparison across national borders. For each state discussed in the book, we highlight fundamental statutory and administrative regulations and substantive provisions pertaining to germline modifications. We show that national legal frameworks are fragmented and outdated, and thus inadequate. We conclude by identifying steps that states can take to clarify and modernize their regulatory frameworks.

---

1. *A DRAFT Governance Framework for Human Genome Editing*, WORLD HEALTH ORGANIZATION [WHO] (2020), https://www.who.int/ethics/topics/human-genome-editing/Governance-framework-for-HGE-Jan2020.pdf.

2. ANDREA BOGGIO ET AL., HUMAN GERMLINE GENOME MODIFICATION AND THE RIGHT TO SCIENCE: A COMPARATIVE STUDY OF NATIONAL LAWS AND POLICIES (Andrea Boggio, Cesare P.R. Romano & Jessica Almqvist eds., 2020) [hereinafter HUMAN GERMLINE GENOME MODIFICATION AND THE RIGHT TO SCIENCE].

3. Australia, Belgium, Canada, China, France, Germany, Israel, Italy, Japan, Mexico, Netherlands, Singapore, South Korea, Spain, Sweden, Switzerland, the United Kingdom, and the United States. *Id.* at 17.

4. G.A. Res. 217 (III) A, Universal Declaration of Human Rights, art. 27 (Dec. 10, 1948).

5. International Covenant on Economic, Social and Cultural Rights art. 15, *opened for signature* Dec. 16, 1966, 993 U.N.T.S. 3 (entered into force Jan. 3, 1976).

6. For a discussion of these instruments, *see* Andrea Boggio et al., *The Human Right to Science and the Regulation of Human Germline Engineering*, 2 CRISPR J. 134, 136 (2019); HUMAN GERMLINE GENOME MODIFICATION AND THE RIGHT TO SCIENCE, *supra* note 2.

I. METHODOLOGY

This article is based on data appearing in various chapters of "Human Germline Genome Modification and the Right to Science: A Comparative Study of National Laws and Policies." The chapters were written by experts, following a template that we developed and handed out at the time the invited experts confirmed their interest in contributing to the project. The template was prepared and distributed to ensure consistency among the various chapters. Among other things, the template asked them to discuss two items: (1) *which* legal sources regulate the subject matter (i.e., constitutional provisions, statutory law, administrative rules, regulations, and guidelines), and (2) *what* those legal sources say about the subject matter, that is, to analyze the substantive provisions expressed by the national regulatory frameworks. The regulation of germline modification was broken down into four steps, corresponding to different stages of the "bench to the bedside" research pipeline: basic research, preclinical research or research with animals, clinical research, and clinical application.[7] We refer to these stages as "subareas."

The analysis presented in this article focuses on some key legal questions:

> For basic research: whether the law defines gametes and embryos; whether research on gametes and embryos (both by creating research embryos and using IVF embryos) is permissible; and whether scientists can modify the genome of gametes and embryos used in research.
>
> For clinical research: whether modified germline tissue can be tested on humans; and how the law classifies these studies.
>
> For clinical applications: whether gene therapy or other interventions based on germline modifications can be offered to patients, and if so, under what conditions.

In this article, we do not discuss supranational legal instruments. However, several synapses refer to the two that are most relevant to HGGM: The Convention for the Protection of Human Rights and Dignity of the Human Being with Regard to the Application of Biology and

7. In this article we do not discuss preclinical research and instead focus on the three other subareas.

Medicine (also called the Oviedo Convention),[8] and the EU's Clinical Trials Regulation.[9]

The Oviedo Convention is a treaty that has been ratified by three of the states included in the study: France, Spain, and Switzerland. Therefore, the provisions of the Oviedo Convention are officially binding on these states. According to the treaty provisions, research on, and *in vitro* modification of, IVF embryos is permitted, but the creation of research embryos is prohibited.[10] In addition, interventions "seeking to modify the human genome" must have "preventive, diagnostic or therapeutic purposes" and not "introduce any modification in the genome of any descendants."[11] In this article, we limit our analysis to the ratification status of the Oviedo Convention in the states that are members of the Council of Europe, but do not discuss its provisions.

The EU Clinical Trials Regulation, set to take effect in late 2021, bans all 27 EU member states from conducting gene therapy trials that can result in modifications to the research subject's germline.[12] This means that no EU member state will be able to authorize clinical trials in which genetic modification technologies are tested on humans. Since what remains uncertain is *when* it will become applicable not *if*, the synopses refer to this Regulation assuming it is already effective.[13]

---

8. Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine [Oviedo Convention], Apr. 4, 1997, ETS no. 164 (entered into force Dec. 1, 1999).

9. Regulation (EU) No 536/2014 of the European Parliament of 16 April 2014 on Clinical Trials on Medicinal Products for Human Use and Repealing Directive 2001/20/EC, 2014 O.J. (L 158) 1, 158 [hereinafter Regulation (EU) 536/2014]. Both instruments are discussed at length in Cesare P. R. Romano, Andrea Boggio & Jessica Almqvist, *The Governance of Human (Germline) Genome Modification at the International and Transnational Levels*, *in* HUMAN GERMLINE GENOME MODIFICATION AND THE RIGHT TO SCIENCE 22, 31; Jessica Almqvist & Cesare P.R. Romano, *The Regulation of Human Germline Genome Modification in Europe*, *in* HUMAN GERMLINE GENOME MODIFICATION AND THE RIGHT TO SCIENCE 155, 193-97.

10. Oviedo Convention, *supra* note 8, art. 18.

11. *Id.* art. 13.

12. The European law currently in effect already prohibits such clinical trials. However, the European law is in the form of a directive, which means member states have some flexibility in implementing it. The regulations remove that flexibility. *See* Council Directive 2001/20/EC of the European Parliament and Council of 4 April 2001 on the Approximation of the Laws, Regulations and Administrative Provisions of the Member States Relating to the Implementation of Good Clinical Practice in the Conduct of Clinical Trials on Medicinal Products for Human Use, 2001 O.J. (L 121) 34 [hereinafter Council Directive 2001/20/EC].

13. Likely they will become effective in late 2020 as soon as the audit of the new clinical trials portal and database is completed. *See Clinical Trial Regulation*, EUR. MEDS. AGENCY, https://www.ema.europa.eu/en/human-regulatory/research-development/clinical-trials/clinical-trial-regulation (last visited Feb 16, 2020).

II. NATIONAL FRAMEWORK SYNOPSES

A. Australia

In Australia, key statutes regulating research on embryos and clinical trials were adopted in the early 2000s and, for the most part, have been left untouched since then.[14] The statutory law and associated guidelines create "a highly restrictive regime"[15] revolving around the prohibition to create research embryos, with "embryo" being defined broadly.[16] Research on supernumerary embryos and gametes, including their modification, is permissible provided the goals of the research are therapeutic and cannot be achieved without using embryos.[17] Gametes cannot be used to create embryos for either research or reproductive purposes.[18] Further, applying germline modifications is considered a criminal offense when "the genome of a human cell [is altered] in such a way that the alteration is heritable by descendants of the human whose cell was altered."[19] The prohibition seems to also extend logically to clinical research because, if undertaken, this research would involve a genome alteration that is able to be passed on "to future generations."[20] The prohibition, however, is not explicit and, as Nicol points out, "[t]he extent to which [the] prohibition [of Section 15] might apply in the research context awaits definitive statutory interpretation."[21]

---

14. *Prohibition of Human Cloning for Reproduction Act 2002 (*Cth) 24 n.3 (Austl.); *Research Involving Human Embryos Act 2002* (Cth) 48 nn.3-4 (Austl.).

15. Dianne Nicol, *The Regulation of Human Germline Genome Modification in Australia*, *in* HUMAN GERMLINE GENOME MODIFICATION AND THE RIGHT TO SCIENCE 543, 560.

16. *See Prohibition of Human Cloning for Reproduction Act 2002* (Cth) s 8 (Austl.); *Research Involving Human Embryos Act 2002* (Cth) s 7 (Austl.) (an embryo is "a discrete entity that has arisen from either: (a) the first mitotic division when fertilisation of a human oocyte by a human sperm is complete; or (b) any other process that initiates organised development of a biological entity with a human nuclear genome or altered human nuclear genome that has the potential to develop up to, or beyond, the stage at which the primitive streak appears; and has not yet reached 8 weeks of development since the first mitotic division").

17. NAT'L HEALTH AND MED. RSCH. COUNCIL, ETHICAL GUIDELINES ON THE USE OF ASSISTED REPRODUCTIVE TECHNOLOGY IN CLINICAL PRACTICE AND RESEARCH 100 (2017).

18. The latter falls under the general prohibition of clinical applications involving germline modifications.

19. *Prohibition of Human Cloning for Reproduction Act 2002* (Cth) s 15 (Austl.). The keyword here is "heritable," which the explanatory memorandum of the law defines as "able to be passed on to subsequent generations of humans." Explanatory Memorandum, Prohibition of Human Cloning for Reproduction and the Regulation of Human Embryo Research Amendment Bill 2006 (Cth) cl 15 (Austl.).

20. *Id.*

21. Nicol, *supra* note 15, at 556 (discussing some limited circumstances where research involving genetic manipulation of embryos might be allowed in Australia).

B. Belgium

Belgium has one of the most liberal regulatory frameworks of germline modification among European nations. It has not ratified the Oviedo Convention because it does not accept the limitations the treaty imposes on human genome modification research. The two essential statutes are the 2003 Law regarding Research on Embryos In Vitro, and the 2007 Law regarding Medically Assisted Reproduction and the Disposition of Embryos and Gametes. An embryo is defined as "a cell or coherent set of cells with the ability to grow into a human being."[22] Basic research on, and modification of, gametes and embryos, whether created for research purposes or supernumerary, are lawful, yet research embryos can be used only if supernumerary embryos are not suitable for that research project.[23] The research must have a therapeutic goal.[24] The statute purportedly allows clinical research on the transfer of modified embryos in humans for the purpose of testing gene therapy that benefits the specific embryo.[25] The same provision also opens the door to clinical applications in the form of gene therapy that is beneficial to the embryo. Even so, the EU Clinical Trials Regulation prohibits this type of clinical research by virtue of Belgium's membership in the EU. In the absence of the permission to run clinical trials, this gene therapy would have to be approved outside of Europe first, and then commercialized in Belgium, which may not be legally possible.[26] The 1998 EU Directive on the legal protection of biotechnological inventions excludes the patentability of "processes for modifying the germ line genetic identity of human beings."[27]

C. Canada

Canada's regulatory framework of human genome modification is generally conservative. The key statute is the 2004 Assisted Human Reproduction Act, which applies throughout the federation, and defines an embryo as "a human organism during the first 56 days of its development following fertilization or creation, excluding any time during which its

22. Loi du 11 mai 2005 relative à la recherche sur les embryons in vitro [Law concerning the investigation on embryos in vitro] (Belg.), M.B., May 28, 2003, http://www.staatsblad.be [hereinafter In Vitro Embryo Research Law of May 11, 2003 (Belg.)].

23. *Id.* art. 4.

24. *Id.* art. 3 (the aim must be "advancing knowledge about fertility, infertility, organ or tissue transplants, the prevention or treatment of diseases").

25. *Id.* art. 5 (providing an exception to the prohibition on implantation research when "the research was carried out with a therapeutic goal for the embryo itself").

26. Regulation (EU) 536/2014, *supra* note 9, art. 90.

27. Directive 98/44/EC of the European Parliament and of the Council of 6 July 1998 on the Legal Protection of Biotechnological Inventions, art. 6, 1998 O.J. (L 213) 13, 18.

development has been suspended, and includes any cell derived from such an organism that is used for the purpose of creating a human being."[28] According to the statute, creating research embryos is a crime,[29] and only supernumerary embryos can be used and modified in basic research. This research must be carried out pursuant to the requirements set in the Tri-Council Policy Statement, "Ethical Conduct for Research Involving Humans," a set of guidelines adopted by the national granting councils.[30] The statement provides that the research must "benefit the embryo"[31] (without further specification of what "benefit" means) and that "embryos exposed to manipulations not directed specifically to their ongoing normal development will not be transferred for continuing pregnancy."[32] This seems to prohibit both clinical trials and clinical applications. Further support of this conclusion comes from the 2004 Assisted Human Reproduction Act, which prohibits altering "the genome of a cell of a human being or *in vitro* embryo such that the alteration is capable of being transmitted to descendants."[33] The statutory language does not expressly mention clinical research and the ambiguity has yet to be clarified. Meanwhile, no basic research using human germline modification in human embryos is being carried out in Canada.[34]

D. People's Republic of China

The People's Republic of China's (China) regulatory framework is under much scrutiny in the aftermath of the He Jianku affair. Its legal system is based on the civil law tradition, with the Communist Party holding supreme political authority. The crucial legal instruments around HGGM were enacted in the 2000s, although the regulation of research on human subjects was substantially reformed in 2016.[35] Neither embryo,

28. Assisted Reproduction Act, S.C. 2004, c 2 (Can.) [hereinafter Assisted Reproduction Act (Can.)].

29. *Id.* art. 5(1)(b).

30. CANADIAN INSTS. OF HEALTH RSCH., NAT. SCIS. AND ENG'G RSCH. COUNCIL OF CANADA, & SOC. SCIS. AND HUMANS. RSCH. COUNCIL OF CANADA, TRI-COUNCIL POLICY STATEMENT: ETHICAL CONDUCT FOR RESEARCH INVOLVING HUMANS (2014), https://www.cmcc.ca/Tri-Council%20Policy%20Statement.pdf.

31. Assisted Reproduction Act art. 12.7(a) (Can.). The statute does not define the term "benefit."

32. *Id.* art. 12.8(c).

33. *Id.*

34. Erika Kleiderman, *The Regulation of Human Germline Genome Modification in Canada*, *in* HUMAN GERMLINE GENOME MODIFICATION AND THE RIGHT TO SCIENCE83, 84.

35. Ren Peitai Ganxibao Yanjiu Lunli Zhidao Yuanze (人胚胎干细胞研究伦理指导原则) [Guiding Ethical Principles for Human Embryonic Stem Cell Research] (promulgated by the Ministry of Sci. and Tech. and Ministry of Health, Dec. 24, 2003), http://www.most.gov.cn/fggw/zfwj/zfwj2003/200512/t20051214_54948.htm (China); Renlei Fuzhu Shengzhi Jishuguifan (人类辅助

zygote, nor gamete are expressly defined. Overall, Chinese law is permissive. Scientists can create research embryos (also with modified gametes) and use supernumerary embryos, but with government oversight.[36] Regarding clinical research, the key regulation only limits research on somatic cells and does not address germline cells.[37] However, the Chinese regulatory framework rejects, in clear terms, clinical applications of germline modifications. Per the Technical Norms on Assisted Reproduction, "gene manipulation of human gametes, zygotes or embryos for reproductive purposes" is prohibited.[38] Further, the Guiding Ethical Principles for Human Embryonic Stem Cell Research prohibit the implantation of embryos that were used for research.[39] Clinical research is logically

---

生殖技术规范) [Technical Norms on Assisted Reproduction] (promulgated by the Ministry of Health, May 14, 2001, rev'd by the Ministry of Health, Oct. 1, 2003), http://www.nhc.gov.cn/bgt/pw10303/200708/68ba58984aba4a44a3bcf74b0c3e2048.shtml (China); Yiliao Jishu Linchuangyingyong Guanlibanfa (医疗技术临床应用管理办法) [Administrative Measures for the Clinical Application of Medical Technology] (promulgated by the Ministry of Health, Mar. 2, 2009), http://www.gov.cn/gongbao/content/2009/content_1388686.htm (China); Ganxibao Zhiji Zhiliang Kongzhi Ji Linchuang Qian Yanjiu Zhidao Yuanze (Shixing) (干细胞制剂质量控制及临床前研究指导原则(试行)) [Guiding Principles for Human Gene Therapy Research and Quality Control of Preparation (Trial)] (promulgated by Ministry of Health, Mar. 20, 2003) (China); Sheji Ren de Shengwu Yixue Yanjiu Lunli Shencha Banfa (涉及人的生物医学研究伦理审查办法) [Ethical Review Guidelines on Biomedical Research Involving Human Subjects] (promulgated by Nat'l Health and Family Planning Comm., Oct. 12, 2016, effective Dec. 1, 2016), http://www.nhc.gov.cn/fzs/s3576/201610/84b33b81d8e747eaaf048f68b174f829.shtml (China).

36. An administrative license issued by the Human Genetic Resources Management Office is needed for the collection, storage, and export of human genetic materials. *See* Renlei Yichuan Ziyuan Guanli Zanxing Banfa (人类遗传资源管理暂行办法) [Interim Administrative Measures for Human Genetic Resources] (promulgated by the Ministry of Sci. and Tech., June 10, 1998), http://www.most.gov.cn/fggw/xzfg/200811/t20081106_64877.htm, cl. 3, 7 (China).

37. Guiding Principles for Human Gene Therapy Research and Quality Control of Preparation (China). When this article was in production, the Chinese Criminal Code was amended to prohibit the implantation of genetically edited or cloned human embryos into human or animal bodies, or the implantation of genetically edited or cloned animal embryos into human bodies." *See* Shao Bowen, *Can China's New Criminal Law Deter the Next He Jiankui?*, SIXTH TONE (Mar. 12, 2021), https://www.sixthtone.com/news/1006904/can-chinas-new-criminal-law-deter-the-next-he-jiankui.

38. Technical Norms on Assisted Reproduction (China), pt. III, para. 9. The same rule is also stated in the Ethical Principles for Human Assisted Reproductive Technology and Human Sperm Bank. Renlei Fuzhu Shengzhi Jishu he Renlei Jingziku Lunli Yuanze (人类辅助生殖技术和人类精子库伦理原则) [Ethical Principles for Human Assisted Reproductive Technology and Human Sperm Bank] (promulgated by the Ministry of Health, May 14, 2001, rev'd by the Ministry of Health, Oct. 1, 2003), http://www.nhc.gov.cn/bgt/pw10303/200708/68ba58984aba4a44a3bcf74b0c3e2048.shtml (China). Lingquiao Song & Rosario Isasi, *The Regulation of Human Germline Genome Modification in the People's Republic of China*, *in* HUMAN GERMLINE GENOME MODIFICATION AND THE RIGHT TO SCIENCE 83, 84.

39. Ethical Guiding Principles on Human Embryonic Stem Cell Research (China) art. 6 ("(1) blastocysts obtained by *in vitro* fertilization, somatic cell nuclear transplantation, single-sex replication technology or genetic modification shall not be cultured for more than 14 d after fertilization

impossible if edited embryos cannot be implanted.[40] Notably, a court found He Jianku's actions were in violation of Chinese criminal law.[41]

E. France

By ratifying the Oviedo Convention in 2011, France adopted a highly restrictive regulatory framework. The chief statute is the Public Health Code, which was amended between 1988 and 1994 to include provisions on research on embryos and assisted reproduction.[42] The Public Health Code, which does not define "embryo," prohibits creating research embryos[43] but permits research on supernumerary embryos, which can be modified.[44] Research must be reviewed and approved by the Biomedicine Agency (*Agence de la Biomédecine*), a public body set by the Bioethics Law.[45] Among the requirements for approval are a showing that the study cannot be done without using embryos and that it has a medical aim and medical relevance.[46] Research on gametes, including their modification, is not expressly regulated, which means that it is not prohibited. Conversely, clinical applications of germline engineering are prohibited by the Civil Code and the Public Health Code.[47] Germline applications

---

or transplantation; (2) the human blastocyst for research shall not be implanted into the reproductive system of a human or any other animal.").

40. Jing-Ru Li et al., *Experiments That Led to the First Gene-Edited Babies: The Ethical Failings and the Urgent Need For Better Governance*, 20 J. ZHEJIANG UNIV. SCI. B., 32, 32–37 (2019). (pointing out that He Jianku's research was not properly approved by an Ethics Committee. He Jianku only received approval from the Ethics Committee of the Shenzhen HarMoniCare Women and Children's Hospital, which was not a registered committee and therefore without the authority to approve the research protocol).

41. Antonio Regalado, *He Jiankui Faces Three Years in Prison for CRISPR Babies*, MIT TECH. REV., (Dec. 30, 2019), https://www.technologyreview.com/s/614997/he-jiankui-sentenced-to-three-years-in-prison-for-crispr-babies/ (discussing He Jianku's criminal conviction). *See also* Henry T. Greely, *CRISPR'd Babies: Human Germline Genome Editing in the "He Jiankui affair"*, 6 J. L. BIOSCIENCES 111, 166 (2019) ("He violated Chinese law by procuring assisted reproduction for HIV carriers through recruiting uninfected men who would then provide blood for testing while falsely claiming to be the research subjects, that kind of fraud on an approval process should be actionable anywhere. The fact that the rule he allegedly circumvented may be an unjust one cannot here excuse his fraud.").

42. Code de la santé publique [C.S.P.] [Public Health Code] art. L2151-2 (Fr.) (The relevant provisions were added to the Code by four laws, collectively known as "Bioethics Laws" or lois de bioéthique: Law No. 94–548 of July 1, 1994; Law No. 94–653 of July 29, 1994; Law No. 94–654 of July 29, 1994; Law No. 88–1138 of December 20, 1988.).

43. C.S.P. art. L2151-2 (Fr.).

44. The modification of supernumerary embryos as part of a research protocol is not expressly prohibited, thus it is permissible.

45. C.S.P. art. L2151-5 (Fr.).

46. *Id*.

47. Code Civil [C. civ.] [Civil Code] art.16-4 (Fr.) (prohibiting any activity that could damage the integrity of the human species); C.S.P. art. L2151-5 (Fr.) ("Embryos on which research was carried on cannot be transferred [in the uterus] with the goal of starting a pregnancy.").

may also be contrary to criminal laws against eugenic practices.[48] Logically, this prohibition appears to extend to clinical research. The Civil Code, however, has an exception for clinical studies that investigate whether germline genome modifications can be used to prevent genetic disease.[49]

F. Germany

More than 25 years ago, the Federal Republic of Germany adopted one of the most restrictive legal regimes in the world on germline cells. While Belgium has not ratified the Oviedo Convention because it deems it too restrictive, Germany has not done so because it deems the convention to be "too liberal," particularly with regard to embryo research.[50] The fundamental statute is the Embryo Protection Act, which defines an embryo as a "human egg cell, fertilized and capable of developing, from the time of fusion of the nuclei, and further, each totipotent cell removed from an embryo that is assumed to be able to divide and to develop into an individual under the appropriate conditions for that."[51] Germline cells are cells "that lead directly from the fertilized egg cell to the egg and sperm cells of the resultant human being and also egg cells from insertion or penetration of the sperm cell until the completion of fertilization by fusion of the nuclei."[52] The law punishes basic research on modified gametes,[53] the creation of research embryos,[54] and any "use" of embryos for any purpose other than their "preservation."[55]

---

48. Code Pénal [C. pén.] [Penal Code] arts. 214-1, 214-3, 214-4 (Fr.).

49. C. civ. art. 16-4 (Fr.) (genetic modifications intended to alter the progeny of a person are prohibited with no "prejudice for research aiming at preventing or treating a genetic disease").

50. Almqvist & Romano, *supra* note 9, at 169.

51. Embryonenschutzgesetz [ESchG] [The Embryo Protection Act], §§ 8.1, 8.2 (Ger.), https://www.gesetze-im-internet.de/eschg/BJNR027460990.html. (Section 8.2 specifies that a fertilized egg is considered an "embryo" in the first 24 hours after the fusion of nuclei unless it is clear that it is not capable of developing beyond the one-cell stage). *See* Timo Faltus, *The Regulation of Human Germline Genome Modification in Germany*, *in* HUMAN GERMLINE GENOME MODIFICATION AND THE RIGHT TO SCIENCE 241, 252.

52. ESchG § 8.3 (Ger.). It is disputed whether this definition covers artificially-created gametes. *See* Faltus, *supra* note 51, at 252.

53. ESchG § 5.4 (Ger.) (clarifying that "any use of it for fertilization has been ruled out").

54. ESchG § 1.1 (Ger.). An interesting aspect of German law is the extraterritorial reach of the criminal provisions of the Embryo Protection Act: German-based scientists are punished even if the actions that are in violation of criminal law took place abroad, as part of a research collaboration. *See* Strafgesetzbuch [StGB] [Penal Code], § 9(2), *translation in* https://www.gesetze-im-internet.de/englisch_stgb/englisch_stgb.html (Ger.); Faltus, *supra* note 51, at 245.

55. ESchG § 1.1 (Ger.). Hypothetically, research that does not result in the destruction of the embryo is permitted. However, the law prohibits modifying the genetic characteristics of human germline cells and, because both clinical research and applications are prohibited, the implant of these embryos is punishable. *Id.* § 5.

G. Israel

Famously hailed as "the quintessential start-up nation,"[56] Israel relies on a vibrant biotechnology sector. It favors innovation in all areas of scientific and technological research, and human genome germline modifications is no exception. The central statute is the Prohibition of Genetic Intervention, which was adopted in 1999 and amended several times since.[57] The statute, which does not define what an "embryo" is, permits the creation of research embryos and research on supernumerary embryos.[58] Both can be modified but, when modified, cannot be used for reproductive purposes. In fact, using "reproductive cells that have undergone a permanent intentional genetic modification (germline gene therapy) to create a person" is punishable with up to four years imprisonment or a fine. [59] This provision clearly prohibits clinical research and applications. Nevertheless, the prohibition against engaging in clinical research is not absolute: "fearing a total ban might hinder medical progress, the Law includes a section that allows the minister of health to permit, through regulations, and as an exception to the overall prohibition, the performance of specific kinds of genetic interventions involving the reproductive use of germ cells that have undergone a genetic modification."[60] This puts Israel in the unique position of having a mechanism in place that would permit clinical research involving germline genome modifications without requiring legislative intervention.

H. Italy

Despite not having ratified the Oviedo Convention, Italy adopted a restrictive legal framework. The key statute is the Medically Assisted Reproduction Law of 2004, which prohibits the creation of research embryos and research on supernumerary embryos. The statute does not define the term "embryo." The use of gametes in research, including their editing, is not expressly prohibited and therefore, can be considered lawful. These gametes cannot be used to create embryos for infertility

56. DAN SENOR & SAUL SINGER, START-UP NATION: THE STORY OF ISRAEL'S ECONOMIC MIRACLE (2011).

57. Prohibition of Genetic Intervention (Human Cloning and Genetic Manipulation of Reproductive Cells) Law, 5759-1999, SH 1697 47 (1998-99), as amended (Isr.). The law was amended in 2004, 2009, and 2016. Vardit Ravitsky & Gali Ben-Or, *The Regulation of Human Germline Genome Modification in Israel*, *in* HUMAN GERMLINE GENOME MODIFICATION AND THE RIGHT TO SCIENCE 568SCIENCE568, 571.

58. Prohibition of Genetic Intervention Law (Isr.); Ravitsky and Ben-Or, *supra* note 57, at 573.

59. Prohibition of Genetic Intervention Law (Isr.).

60. Ravitsky & Ben-Or, *supra* note 57, at 573.

treatment.[61] On the one hand, the law permits experimenting on embryos by modifying them if the goal is diagnostic or therapeutic (protecting the health and development of the embryo), and no alternatives are available.[62] This means that basic research intended to benefit an embryo is lawful. On the other hand, clinical research is prohibited both by domestic law[63] and EU law. This means that the embryos that were "treated" (i.e., modified in research) as part of research cannot be used in clinical trials. The statute also prohibits destroying embryos,[64] which, since they cannot be implanted, are being stored *sine die*. By contrast, clinical applications involving germline modifications are not prohibited.[65] However, since this form of gene therapy cannot be authorized in Europe, only gene therapies tested and approved outside of Europe could be offered to Italian patients if these therapies are ever developed.

I. Japan

The Japanese regulatory environment is also restrictive. The key instruments are the Act on Regulation of Human Cloning Techniques,[66] and the Fundamental Policy Regarding Handling of Human Embryos,[67] which are issued by the executive. The act defines an embryo as "a cell (except for a Germ Cell) or a cell group which has the potential to grow into an individual through the process of development *in utero* of a human or an Animal and remains at a stage prior to placental formation."[68] The policy prohibits creating research embryos but permits research on supernumerary embryos, including modifying their genome as long as the purpose of the research is therapeutic.[69] Research on gametes, including their genome modification, is also permitted in Japan but said research cannot be

61. Legge 19 febbraio 2004, n.40, G.U. Feb. 24, 2004, n.45 [Rules on Medically Assisted Procreation Act] (It.).

62. *Id.*

63. Decreto legislativo 24 giugno 2003, n.211, G.U. Aug. 9, 2003, n.184 (It.) (implementing Council Directive 2001/20/EC).

64. L. n. 40/2004 (It.).

65. Ludovica Poli, *The Regulation of Human Germline Genome Modification in Italy*, *in* HUMAN GERMLINE MODIFICATION AND THE RIGHT TO SCIENCE 335, 355–56.

66. Hito ni kansuru kurōn gijutsu-tō no kisei ni kansuru hōritsu [Act on Regulation of Human Cloning Techniques Act], Law No. 146 of 2000, art. 1(i) (Japan).

67. Sōgō kagaku gijutsu kaigi [Council for Science and Technology Policy], *Hito hai no toriatsukai ni kansuru kihon-teki kangaekata [Fundamental Policy Regarding Handling of Human Embryos]* (July 23, 2004), https://www8.cao.go.jp/cstp/tyousakai/life/haihu39/siryo5-1-1.pdf (Japan).

68. Act on Regulation of Human Cloning Techniques Act, art. 2 (Japan).

69. *Fundamental Policy Regarding Handling of Human Embryos*, *supra* note 67, art. 9.2 (implying that research embryos can only be used in *in vitro* experiments to study a disease).

used to create an embryo.[70] Although, the policy does prohibit clinical research to develop "gene therapy" using germline genome editing. The definition of "gene therapy" ("the administration of a gene or cells into which a gene was transferred for the purposes of treatment and prohibition of a disease") creates a loophole.[71] According to Ishii, clinical research that uses only nucleases in the form of mRNA or protein to cause the germline modification does not constitute germline cell "gene therapy," and thus is not prohibited.[72] However, ministerial guidelines ban clinical applications and is a further obstacle to clinical research because they prohibit the transfer of modified embryos to a uterus.[73]

J. Republic of Korea

The Republic of Korea (South Korea) is, besides Israel, one of the states that invests the most in research and investment. However, when it comes to HGGM, South Korea has a conservative regulatory framework. The key statute—the Bioethics and Safety Act, which was adopted in 2005 and then revised in 2008, 2012, and 2015—defines an embryo as "a fertilized human ovum or a group of [segmented] cells divided during a period from the time such ovum is fertilized until the time all organs are embryologically formed."[74] The statute prohibits and criminally sanctions the creation of research embryos,[75] but permits research and modification of supernumerary embryos and gametes.[76] Research must have a therapeutic focus or be otherwise approved by the President upon review of the National Bioethics Committee.[77]

---

70. Ministry of Education, Culture, Sports, Science and Technology [MEXT], Hito iPS saibō matawa hito soshiki kan saibō kara no seishoku saibō no sakusei o okonau kenkyū ni kansuru shishin [Guidelines on Research into Producing Germ Cells from Human Induced Pluripotent Stem Cells or Human Tissue Stem Cells], MEXT Public Notice No. 88 of 2010, art. 6, *translated in* MEXT's online database, https://www.lifescience.mext.go.jp/files/pdf/n1567_02r2.pdf (Japan).

71. Tetsuya Ishii, *The Regulation of Human Germline Genome Modification in Japan*, *in* HUMAN GERMLINE MODIFICATION AND THE RIGHT TO SCIENCE 441, 459 (quoting article 2.1 of the Ministry of Health, Labor and Welfare [MHLW], *Idenshi chiryō-tō rinshō kenkyū ni kansuru shishin [Guidelines for Clinical Research Such as Gene Therapy]* (Aug. 27, 2015), MHLW Notification No. 344 (Japan)).

72. *Id.* at 460.

73. MEXT, Tokutei hai no toriatsukai ni kansuru shishin [Guidelines on the Handling of Specified Embryos], MEXT Public Notice No. 83 of 2009, art. 7, https://www.lifescience.mext.go.jp/files/pdf/30_82.pdf (Japan). ("For the time being, specified embryos not prescribed in the provisions of Article 3 of the Act may not be transferred to human or animal uterus.").

74. Bioethics and Safety Act, amended by Act No. 12844, Nov. 19, 2014 (S. Kor.), *translated in* Korea Legislation Research Institute's online database, https://elaw.klri.re.kr/eng_mobile/viewer.do?hseq=33442&type=part&key=36.

75. *Id*. art. 23.

76. *Id.* art. 29.

77. *Id*.

The use of either embryos or gametes for reproductive purposes is prohibited. This is because the statute expressly prohibits "gene therapy" applied to human embryos, ovum, sperm, or fetuses.[78] The letter of the law makes it clear that any treatment involving editing intervention of germline cells would be classified as "gene therapy."[79] A plain reading of the same statute leads to the conclusion that clinical trials on human germline genome modification are prohibited even if the statute that regulates clinical trials (the Pharmaceutical Affairs Act) does not expressly prohibit these types of studies.[80] If embryos cannot be implanted, then clinical trials cannot be carried out. Ultimately, as Kim and Joly point out, "a degree of confusion about research studies on human germline genome modification" remains.[81]

K. Mexico

Mexico's relevant statute is a federal law—the 2008 General Health Law.[82] The statute defines germline cells as "male and female reproductive cells that are capable of giving origin to an embryo" and an embryo as "the product of conception from the moment of it, and until the end of the twelfth gestational week."[83] "Conception" is not defined, so it is unclear whether embryos created *in vitro* fall under the scope of the statute.[84] Many of the 32 states of Mexico have enacted restrictive legislation.[85] Eighteen have constitutions protecting life from "conception."[86] Donation of eggs and sperm is prohibited for any purpose, including research, but

78. *Id.* art. 47.

79. *Id*. art. 2 (defining gene therapy as "a series of procedures to alter genes in the body for the purpose of preventing or treating a disease or to transfer hereditary substances or cells to which hereditary substances are introduced to the body"). Interestingly, the definition of gene therapy of the Regulation on Review and Authorization of Biological Products differs, the major difference being that gene therapy is defined as a product rather than a practice. *See* Hannah Kim & Yann Joly, *The Regulation of Human Germline Genome Modification in the Republic of Korea*, *in* HUMAN GERMLINE GENOME MODIFICATION AND THE RIGHT TO SCIENCE 500SCIENCE500, 507.

80. Bioethics and Safety Act (S. Kor.); Pharmaceutical Affairs Act, amended by Act. No. 11690, March 23, 2013, art. 34(5) (S. Kor.), *translated in* Korea Legal Research Institute's online database, https://elaw.klri.re.kr/eng_service/lawView.do?hseq=40196&lang=ENG.

81. Kim & Joly, *supra* note 79, at 508 (giving the example that purely enhancement-oriented research may not be prohibited).

82. Ley General de Salud [LGS], Diario Oficial de la Federación [DOF] 07-02-1984, 19-02-2021 (Mex.) (Mexico lacks specific legislation regulating assisted reproductive technology and genetic engineering).

83. LGS, art. 314 (Mex.).

84. María de Jesús & Medina Arellano, *The Regulation of Human Germline Genome Modification in Mexico*, *in* HUMAN GERMLINE GENOME MODIFICATION AND THE RIGHT TO SCIENCE 129, 137.

85. *Id.* at 142.

86. *Id.*

gametes collected for IVF and no longer needed for reproductive uses, can be researched.[87] Research embryos cannot be created because fertilizing eggs for purposes other than reproduction is a crime.[88] By contrast, research on embryos created for reproductive purposes, including their modifications, can be carried out legally if the goal is therapeutic.[89] Whether these embryos can be implanted is unclear. Clinical research is not expressly prohibited and may be lawful when intended to benefit the embryo.[90] The same may be true also for clinical applications. This conclusion is reinforced by Mexico's handling of a mitochondrial replacement procedure that took place in 2016 at a fertility center authorized by the federal drug regulatory agency. In the aftermath of the procedure, the government reviewed the events and concluded that, although not expressly allowed by the law, carrying out the procedure was not in violation of federal law.[91]

L. Netherlands

The Netherlands, which signed but never ratified the Oviedo Convention, adopted its key statute—the Embryo Act—in 2002.[92] An embryo is defined as a "cell or coherent whole of cells with the capacity to grow into a human being."[93] The statute prohibits the creation of research embryos,[94] but permits research on gametes and on supernumerary embryos

87. LGS, art. 330 (Mex.).

88. Código Penal Federal [CPF], art. 154, Diario Oficial de la Federación [DOF] 14-08-1931, 24-01-2020 (Mex.). In the study conducted by Munne and his colleagues, embryos were created (*in vivo*) for research purposes. The study was approved by the state authorities. *See* Santiago Munné, *First PGT-A Using Human In Vivo Blastocysts Recovered by Uterine Lavage*, 35 HUM. REPROD. 70, 70-80 (2020).

89. Reglamento de la Ley General de Salud en Materia de Investigación para la Salud [RLGSMIS], art. 56, Diario Oficial de la Federación [DOF] 06-01-1987, 02-04-2014 (Mex.) (embryo research is lawful if it aims to "solve sterility problems that cannot be solved in any other way, respecting the couple's moral, cultural and social point of view, even if it differs from that of the investigator"). According to Medina Arellano, "supernumerary IVF embryos are often used for basic science research in private and public health research settings." Jesús & Arellano, *supra* note 84, at 148.

90. *Id.* at 151 (stating that "since genetic engineering on IVF human embryos is not prohibited when it is carried out for the benefit of the embryo or fetus, it could be inferred that it is permitted. In addition, if genetic modification of the human germline leads to a benefit to the embryo/fetus, it can be said that clinical application can be allowed").

91. *Id.* at 151–152.

92. *Chart of Signatures and Ratifications of Treaty 164*, COUNCIL OF EUR., https://www.coe.int/en/web/conventions/full-list/-/conventions/treaty/164/signatures (last visited Feb. 13, 2021); Wet van 20 juni 2002, Stb. 2002 (Neth.) [hereinafter Embryo Act (Neth.)].

93. Embryo Act (Neth.), art. 1.c.

94. *Id.* art. 24.a.

that are "likely to lead to new insights in the field of medical science."[95] Basic researchers can modify gametes and embryos, but neither can be implanted or used to create embryos.[96] As a member of the EU, clinical research is prohibited.[97] Clinical applications are also prohibited because modified gametes and embryos cannot be used for reproductive purposes; therefore, a pregnancy cannot be initiated using modified germline tissue.[98]

M. Singapore

With biotech expected to be a "key driver" of the future economy,[99] Singapore's regulatory system is among the most permissive. The primary regulatory instruments are guidelines issued by the Bioethics Advisory Committee, which is appointed by the executive branch of government.[100] These guidelines define an embryo as "the beginning of an organism in the early stages of development; a stage (between the ovum and the foetus) in the prenatal development of a mammal."[101] According to these guidelines, basic scientists can create research embryos or use supernumerary embryos, and then can modify either of them *in vitro*.[102] The creation of research embryos is, however, authorized by the Ministry of Health only on a case-by-case basis, provided the research has strong scientific merit, shows potential therapeutic benefits, and there is no acceptable alternative.[103] Clinical research involving genome-editing techniques is considered to be research into "medicinal products" as defined by the Medicines Act,[104] and is prohibited. While not prohibited by statute, in 2005 the Bioethics Advisory Committee adopted an advisory opinion that imposed a moratorium on therapeutic applications and, consequently, research of germline genetic modification.[105] In 2014, the Bioethics Advisory Committee appointed a Germline Modification

95. *Id.* at 10.a, 10.b; Wet van 26 Februari 1998, Stb. 1998, arts. 14.1, 16 (Neth.).

96. Embryo Act (Neth.), art. 24.g (prohibiting "deliberately modifying the genetic material of the nucleus of human germ cells with which a pregnancy will be established").

97. Regulation (EU) 536/2014, *supra* note 9, art. 90.

98. Embryo Act (Neth.), art. 24.g.

99. Linette Lai, *Biotech Expected to be Key Driver of Future Economy*, STRAITS TIMES (2018), https://www.straitstimes.com/singapore/biotech-expected-to-be-key-driver-of-future-economy (last visited Feb 13, 2020).

100. BIOETHICS ADVISORY COMM., ETHICAL, LEGAL AND SOCIAL ISSUES IN HUMAN STEM CELL RESEARCH, REPRODUCTIVE AND THERAPEUTIC CLONING (2002) (Sing.).

101. *Id*. at Glossary-2.

102. *Id*. at 3.

103. *Id.* at 30

104. Medicines Act, 1975, c. 176, § 3 (Sing.), https://sso.agc.gov.sg/Act/MA1975.

105. BIOETHICS ADVISORY COMM., *supra* note 100, at 10.

Working Group to review the status quo. To date, no recommendation has been adopted.[106]

N. Spain

In 2000, Spain ratified the Oviedo Convention, which was incorporated into Spanish law, and in 2007 it adopted its key statute, the Biomedical Research Law. The Biomedical Research Law adopts the unusual distinction between embryos and pre-embryos.[107] The embryo is "a fertilized oocyte [that] is found in the uterus of a woman" up to 56 days of development. A pre-embryo is a group of cells that is *in vitro* and "the result of the progressive division of the oocyte from the time it is fertilized until 14 days after." From the standpoint of comparative legal analysis (and science), pre-embryos are, to all effects, embryos, and we will treat them as such in this part. With this caveat in mind, Spanish law permits gamete research and modification provided they are not used for reproductive purposes.[108] The creation of research embryos is prohibited,[109] but research on supernumerary embryos is permitted with less restrictions in terms of scope of inquiry.[110] These embryos, however, cannot be implanted.[111] By contrast, a different provision of the law permits therapeutic interventions on embryos.[112] This is not research, as the title of the law indicates, but gene therapy. This gene therapy does not extend to genome modifications because the genome of these embryos cannot be modified.[113] The law is silent about implanting these embryos in the uterus after the interventions. yet logically they must be implanted, or the purpose of the intervention would be moot. It is permissible to perform clinical research by monitoring the embryos in the uterus that underwent therapy, but again the embryos' genomes must have not been modified.[114]

106. Calvin W. L. Ho, *The Regulation of Human Germline Genome Modification in Singapore*, *in* HUMAN GERMLINE GENOME MODIFICATION AND THE RIGHT TO SCIENCE, 516, 524.

107. *See* Cinzia Piciocchi & Lucia Martinelli, *The Change of Definitions in a Multidisciplinary Landscape: The Case of Human Embryo and Pre-embryo Identification*, 57 CROATIAN MED. J. 510, 515 (2016) (discussing the distinction).

108. B.O.E. 2006, 14, art. 14 (Spain).

109. B.O.E. 2007, 159, preamble (Spain).

110. B.O.E. 2006, 14, art. 13 (Spain). Researchers can modify embryos and investigate therapeutic and nontherapeutic aspects.

111. B.O.E. 2006, 14, art. 14 (Spain).

112. *Id.* ("Interventions must treat pathologies with a precise diagnosis, with a serious or very serious prognosis, and that offer reasonable possibilities of improvement or cure.").

113. *Id.* (Requiring that "non-pathological hereditary characteristics are not modified and that the selection of individuals or race is not sought"). This is a clinical application but not germline modification.

114. B.O.E. 2015, 1090, art. 17.3 (Spain). ("Clinical trials with gene therapy medicinal products that cause changes in the gene identity of the person's germline are prohibited."). They are

Clinical applications of germline modifications are expressly prohibited.[115]

O. Sweden

Sweden, which has not ratified the Oviedo Convention, has a regulatory framework more liberal than many other European states. Basic research involving germline modifications can be carried out on gametes, supernumerary embryos, and research embryos. Key terms, like embryo or gamete, are not defined. Clinical research is prohibited both by the EU Clinical Trials Regulation and the Genetic Integrity Act—the latter of which is the leading statute in Sweden in the area of gene editing.[116] The same statute classifies clinical applications of germline engineering as "gene therapy" and prohibits them.[117] The two prohibitions are triggered when germline modifications "that can be inherited" (clinical trials) or that "are intended to bring about genetic changes that can be inherited" (clinical applications).[118] The language in the two provisions differ in that "intent" is only required in the latter case. The definition of "gene therapy" also assumes that the patient is affected by a "genetic disease." A plain reading of the statute seems to exclude nontherapeutic interventions—those purely aimed at enhancement—from the scope of the prohibition. There is also a general prohibition to implant gametes and fertilized eggs that have been used in research.[119] In 2017, the Swedish National Council on Medical Ethics recommended revision of the law in light of the latest scientific developments,[120] but no revision has been made to date.

---

also prohibited as a matter of EU Regulation on Clinical Trials. B.O.E. 2007, 159, art. 74 (Spain). (punishing the "carrying out of any intervention aimed at the introduction of a modification in the genome of the descent").

115. For a more liberal interpretation of Spanish law, *see* Iñigo de Miguel Beriain & Carlos María Romeo Casabona, *The Regulation of Human Germline Genome Modification in Spain*, *in* HUMAN GERMLINE GENOME MODIFICATION AND THE RIGHT TO SCIENCE 358, 375 ("[W]e believe that in Spain basic and clinical research using germline modification technologies and clinical application of these techniques are legal as long as they do not involve the *introduction of new genetic material* into the human genome, nor *intend to change the human genome* (even if they cause this final effect).") (emphasis added).

116. 3-5 § LAG OM GENETISK INTEGRITET M.M (Svensk författningssamling [SFS] 2006:351) (Swed.). ("Experiments for the purposes of research or treatment that entail genetic changes that can be inherited in humans may not be carried out.").

117. *Id.* ("Treatment methods that are intended to bring about genetic changes that can be inherited in humans may not be used.").

118. *Id.*

119. *Id.*

120. Tillsätt en Parlamentarisk Utredning för att se över Lagstifningen på Genteknikområdet [Letter on the Study of Legislation for New Genetic Engineering], Swedish National Council on Medical Ethics (Jun. 7, 2018) (Switz.).

P. Switzerland

The regulatory approach of Switzerland, which has ratified the Oviedo Convention in 2008, is restrictive, starting from the Federal Constitution protecting human beings "against the misuse of reproductive medicine and gene technology."[121] The relevant statutes provide the following definitions: germline cells are defined as "reproductive cells (including their precursor cells), impregnated ova and embryonic cells whose genetic material can be passed on to offspring;"[122] an embryo is defined as "the developing offspring from the time of pronuclear fusion until the end of organogenesis";[123] and a surplus embryo is defined as "an embryo produced in the course of an *in vitro* fertilization (IVF) procedure that cannot be used to establish a pregnancy and therefore has no prospect of survival."[124] The creation of research embryos and the storage of a fertilized egg or embryo—for purposes other than assisted reproduction—is a criminal offense.[125] Intentional germline modifications are also punished criminally.[126] Somewhat less severe, supernumerary embryos may not be used in research. Clinical research and clinical applications are also restricted because of the general prohibitions against both modifying the genetic makeup of gametes and initiating a pregnancy with an edited embryo or an embryo resulting from edited gametes.

Q. United Kingdom

The United Kingdom's regulatory framework is highly supportive of research involving germline genome modification, particularly now that the state is no longer bound by the EU Clinical Trials Regulations after Brexit.[127] The main authority, the Human Fertilisation and Embryology Act of 1990, provides definitions of both "embryos" and

121. BUNDESVERFASSUNG [BV], [CONSTITUTION] Apr. 18, 1999, SR 101, art. 119 (Switz.).

122. BUNDESGESETZ ÜBER DIE MEDIZINISCH UNTERSTÜTZTE FORTPFLANZUNG [FEDERAL ACT ON MEDICALLY ASSISTED REPRODUCTION] Dec. 18, 1998, RS 810.11, art. 2 (Switz.).

123. *Id.*

124. BUNDESGESETZ ÜBER DIE FORSCHUNG AN EMBRYONALEN STAMMZELLEN [FEDERAL ACT ON RESEARCH INVOLVING EMBRYONIC STEM CELLS] Dec. 19, 2003, RS 810.31, art. 2 (Switz.).

125. Federal Act on Medically Assisted Reproduction, art. 29, para. 1-2 (Switz.).

126. *Id*. ("Any person who genetically modifies a germline cell or an embryonic cell shall be punished with reclusion not exceeding three years or a monetary penalty. The same penalty shall apply to any person who uses a genetically modified reproductive cell for impregnation or uses a similarly modified impregnated ovum for further development into an embryo.").

127. The United Kingdom is also a member of the Council of Europe but did not ratify the Oviedo Convention. Almqvist & Romano, *The Regulation of Human Germline Genome Modification in Europe*, *supra* note 9, at 170.

"gametes."[128] Research on gametes, the creation of research embryos, and research on supernumerary embryos are all lawful.[129] All three can further be modified. Clinical research is not permissible because the Human Fertilisation and Embryology Authority, which supervises clinical research, cannot issue "therapeutic licenses."[130] Embryos can be used in basic research upon the issuance of a "research license," but this license does not authorize their use for treatment. That can only occur if a treatment license is issued. Currently, the Human Fertilisation and Embryology Authority does not have the power to issue a treatment license, which means that both clinical research and applications are not permitted. However, the path that has led to the approval of mitochondrial donation for therapeutic purposes could be followed in the future.[131] For that, parliamentary debate and legislative reform would be needed, which may well take place in the immediate future.

R. United States

The regulatory framework of the United States is fragmented because of the limited reach of federal laws and regulations. States have the power to define what an embryo is and to draw the boundaries of the legality of basic research on gametes and embryos. Several states have adopted a variety of approaches to exercise this power, ranging from banning all forms of basic research to allowing the creation and modification of research embryos.[132] Federal law plays a limited role in areas such as embryo research funding and clinical research. Regarding embryo research funding, the so-called Dickey-Wicker Amendment of 1996 prohibits using federal funds to create, destroy, or knowingly injure human embryos.[133] Nevertheless, private or state funds (where permitted) can be used to create embryos, also with modified gametes, and to carry out basic research on them.[134] Clinical research is prohibited because the gene therapy approval agency—the Food and Drug Administration (FDA)—cannot accept applications for clinical trials involving modified embryos

128. Human Fertilisation and Embryology Act 1990, § 1 (Eng.).

129. James Lawford Davies, *The Regulation of Human* Germline Genome Modification in the United Kingdom, *in* HUMAN GERMLINE MODIFICATION AND THE RIGHT TO SCIENCE, 217, 226-28 (Andrea Boggio, Cesare P.R. Romano & Jessica Almqvist eds., 2020).

130. *Id.* at 230.

131. *Id*. at 233-40.

132. Kerry Lynn Macintosh, *The Regulation of Human Germline Genome Modification in the United States*, *in* HUMAN GERMLINE GENOME MODIFICATION AND THE RIGHT TO SCIENCE, 103, 113–115, 124 (Andrea Boggio, Cesare P.R. Romano & Jessica Almqvist eds., 2020).

133. *Id.* at 121.

134. Germline modification basic research can take place in various states. *Id.* at 122-123.

or embryos created using modified gametes.[135] There is no formal prohibition of clinical applications at the federal level,[136] yet because the FDA cannot green-light clinical research, no FDA-approved germline clinical application can be offered to patients. Under the FDA, doing otherwise would be illegal under federal law because gene therapy must be approved prior to marketing.[137]

III. FINDINGS

Our study reveals a highly fragmented regulatory landscape. To date, no state has enacted truly comprehensive legislation on gene editing. By "comprehensive legislation" we mean a regulatory framework that regulates *all* segments of the research pipeline "from bench to bedside" (e.g., basic research on gametes and embryos; clinical trials with human participants; and clinical applications of germline genome editing). Instead, many states have approached the issue in a piecemeal fashion, opting to regulate individual segments. Some do not regulate all segments of the research pipeline expressly,[138] or they fail to define key terms,[139] or they use key terms inconsistently across the different segments, resulting in incoherent regulatory frameworks. Vagueness and ambiguity are particularly concerning, considering that violations are punished with heavy penalties, including criminal ones, in all the states included in our study. Moreover, these legal frameworks generally predate 2012,[140] the year Wired Magazine labeled the "Great CRISPR

135. The FDA has stated that it considers any use of CRISPR/Cas9 gene editing in humans to be gene therapy. U.S. Food & Drug Admin., *Information About Self-Administration of Gene Therapy* (2017), https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/information-about-self-administration-gene-therapy.

136. Macintosh, *supra* note 132, at 125.

137. *Id.* Interestingly, in 2019 California enacted a consumer protection statute mandating that gene therapy kits are sold with a label that states that they are not intended for self-administration. This is the first statute expressly addressing CRISPR-based applications in the United States. S.B. 180, 2019-2020 Sess. (Cal. 2019).

138. The regulation of clinical trials is affected by significant gaps or vagueness in Australia, Canada, China, Korea, and Mexico. Mexico and Spain do not have clear rules as to whether embryos that were used in research can be implanted (this is research that benefits the embryos). The laws of Belgium, France, and Italy, which prohibit clinical research but not clinical application, do not discuss under what conditions these applications can be offered to patients in the absence of a pathway to regulatory approval.

139. E.g., China, France, Israel, Italy, Sweden. In the United States, embryos and gametes are not defined under federal law.

140. On August 17, 2012, Science Magazine published a paper co-authored by a group of seven scientists that included Jennifer Doudna and Emmanuelle Charpentier, which is credited for framing CRISPR/Cas-9 as a gene editing tool. S*ee* Martin Jinek et al., *A Programmable Dual-RNA-Guided DNA Endonuclease in Adaptive Bacterial Immunity*, 337 SCI. 816 (2012), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6286148/pdf/nihms-995853.pdf.

Quake."[141] Human genome modifications are regulated with legal instruments dating back to the 1990s and early 2000s. Few have updated their regulatory framework after 2012.[142]

Overall, research on human embryos is the most heavily regulated subarea and has the most advanced regulations. That is unsurprising since artificial reproductive technologies had already taken off in the 1970s and the legal status of embryos has been debated for even longer. Here, national laws tend to be more precise and compelling than those regulating other subareas. Indeed, for each state surveyed, it is possible to say whether research embryos can be created, under what conditions they can be used in research, and/or whether IVF embryos can be used in research and under what conditions.

However, other more advanced aspects of embryo research are less clearly regulated. For instance, it is often hard to tell whether human embryos can be modified using CRISPR/Cas-9 and similar techniques, or whether research on human germline genome modification is permissible only with therapeutic or enhancement-oriented goals, an issue actively debated in policy conversations on germline editing.

Research on gametes is regulated with less depth. National regulatory frameworks do not often discuss whether, and under what conditions, gametes can be used for research.[143] In theory, according to the legal principle that "what is not prohibited is allowed," one could infer that research on gametes is permitted even when it is prohibited. Making inferences in such a confusing and vague legal landscape, however, is hazardous, especially since many statutes include criminal sanctions.

Clinical research on modified germline tissue appears to be prohibited in all states included in our study. The EU Clinical Trials Regulation clearly prohibits "gene therapy clinical trials … which result in modifications to the subject's germ line genetic identity."[144] Surprisingly, this degree of clarity is rare. Few states expressly prohibit clinical research or studies. They would rather leave scientists and legal advisors to infer the prohibition, either from the fact that the implantation in the uterus of

141. Megan Molteni, *The WIRED Guide to Crispr*, WIRED (Mar. 12, 2019, 6:00 AM), https://www.wired.com/story/wired-guide-to-crispr/.

142. The addition or amendment of regulatory instruments dealing with basic research on germline tissue, clinical trials, or application of gene therapy took place in Canada, France, Japan, Korea, Switzerland, and the United States. Meaningful policy debates took place in the Netherlands.

143. It is to be noted that the prohibition against creating research embryos has ramifications for basic research on gametes. Where creating a research embryo is prohibited, research on modified gametes must stop before fertilization. Similarly, where clinical applications are prohibited, modified gametes cannot be used to create embryos for reproductive purposes.

144. Regulation (EU) 536/2014, *supra* note 9, art. 1.

modified embryos (whether research or supernumerary embryos) is prohibited, or from the fact that the use of modified gametes in fertilization is prohibited. The prohibition to use modified gametes and embryos to initiate a pregnancy makes clinical trials impossible since testing germline modifications requires using modified germline tissue to initiate a pregnancy in a research subject (particularly when embryos have reached the fourteenth day of embryonal development and can no longer by cultivated *in vitro*). For the sake of argument, one can object that, at least in theory, clinical trials testing *in vivo* germline modifications remain possible. The prohibition of clinical trials can also be inferred from the fact that clinical applications, such as making available germline gene therapy to patients, are prohibited as long as enrolling a patient in a clinical trial is equated to offering a germline application to that patient. If the latter is prohibited, the former is also prohibited.

Clinical applications are prohibited in several states. In states where they are not prohibited, HGGM is prohibited if it creates "heritable" traits, but it is allowed if it is "intended to" benefit the embryo or treat "serious conditions."[145] These undefined expressions create further uncertainty.[146] Take the case of "heritability," which is at the core of many national regulations, and of ethical concerns about "hacking humanity."[147] Gene therapies involving germline modifications must be designed so that the pregnancy is carried out to full term. Depending on what was modified and how it was modified, the newborn might, but not always, carry the genes in the modified form. If the newborn does, is the germline modification still heritable if the newborn is sterile or not interested in reproducing, or is the newborn condemned by disease to die before reaching reproductive age? And what if the heritability of the modification was not intentional? Should intent matter? It definitely does where criminal sanctions are applied, but should it also matter where violations of HGGM regulations are not criminally sanctioned?

Finally, several states require research to pursue only therapeutic goals.[148] The requirement to pursue therapeutic goals is often worded broadly, without further details. In some cases, therapeutic goals are limited to treating infertility or generating knowledge about genetic

145. Erika Kleiderman et al., *The 'Serious' Factor in Germline Modification*, 45 J. MED. ETHICS 508, 512 (2019).

146. *Id.* at 510.

147. *Id.* at 508.

148. L. n. 40/2004 (It.). This is not mentioned in China, Israel, Spain, Sweden, and the United States. It is also not mentioned in Germany and Switzerland, but in both states basic research with embryos is prohibited.

disorders.[149] That would rule out basic inquiries into enhancement-oriented research. In other cases, such as the one of Belgium, enhancement-oriented research is prohibited as a form of eugenics. There, "research or treatments of a eugenic nature, that is focused on selection or amplification of non-pathological genetic characteristics of the human species" is prohibited.[150] In a handful of states, research must pursue therapeutic goals, provided the beneficiary of the therapy is the embryo itself. For instance, in Italy, although human embryos cannot be used for research, if the research benefits the embryo, it is permitted.[151] In Spain, interventions that benefit the embryo are considered permissible gene therapy.[152] Belgium permits implanting embryos used in research that benefits the embryo itself.[153] In Mexico, genetic engineering on IVF human embryos is not prohibited when it is carried out for the benefit of the embryo.[154] Further, in Italy and Spain, interventions on embryos cannot alter the genome of the embryo.[155] This is not true in Belgium and is unclear in Mexico.[156]

Limiting research only to those instances that benefit the embryo researched is problematic. Besides complicating further regulations that are already confusing and contradictory, it causes two major practical problems. First, it is scientifically difficult to imagine how research could be beneficial to the embryo without altering its genome. Second, the logical consequence of saying that research must benefit the embryo researched is that it makes it unlawful to destroy it in the process of researching or afterwards. If the embryo cannot be destroyed, then there are only two possible outcomes. The first one is that it is implanted in the uterus. Where this is possible, clinical applications of germline

149. *See* In Vitro Embryo Research Law of May 11, 2003 (Belg.) (research must have "a therapeutic objective or aims to advance knowledge in matters of fertility, sterility, organ or tissue transplants, prevention or treatment of diseases"); C. Civ., art. 16-4 (Fr.). ("to prevent genetic disease"); Jesús & Arellano, *supra* note 84, at 140 (Mexico: "to solve sterility problems"); Embryo Act (Neth.), art. 10 ("new insights in the field of medical science"); Davies, *supra* note 129, at 225-26 (the United Kingdom: where advancing the understanding of embryo development along with therapeutic goals are acceptable goals); *see also* Macintosh, *supra* note 132.

150. In Vitro Embryo Research Law of May 11, 2003 (Belg.).

151. Poli, *supra* note 65, at 350.

152. Beriain & Casabona, *supra* note 115, at 361-62.

153. Guido Pennings, *The Regulation of Human Germline Genome Modification in Belgium, in* HUMAN GERMLINE GENOME MODIFICATION AND THE RIGHT TO SCIENCE 266, 274 (Andrea Boggio, Cesare P.R. Romano & Jessica Almqvist eds., 2020).

154. Jesús & Arellano, *supra* note 84, at 140.

155. Poli, *supra* note 65, at 350; Beriain & Casabona, *supra* note 115, at 362.

156. In Vitro Embryo Research Law of May 11, 2003 (Belg.), art. 5; Jesús & Arellano, *supra* note 84, at 151.

modifications are lawful.[157] Then, logically, clinical research should be lawful too, to ensure that these techniques are tested before being offered to patients. This might be the case in Mexico.[158] If embryos that have been manipulated during research cannot be destroyed and cannot be transferred in the uterus, then the only option left is cryopreserving them in perpetuity, which is an absurdity and a waste. Overall, it seems that statutory language contemplating a benefit for the embryo is, at best, difficult to comply with, or, at worst, meaningless.

IV. A WAY FORWARD

As long as states at the leading edge of human genome modification research do not adopt modern and comprehensive regulatory frameworks, human germline genome modification will remain regulated inconsistently and disjointedly, with gaps, contradictions, and uncertainties.[159] Since the advent of CRISPR, those states that have attempted reform of existing regulatory frameworks have simply tweaked existing frameworks instead of overhauling them.[160] This has magnified inconsistencies and increased the number of possible interpretations. If it was difficult for the legal experts who wrote the book chapters in the edited collection to answer some of the straightforward questions we asked, one can guess how perplexed scientists must be. The confusion does not work to the advantage of both those who would like to shield human embryos from manipulation and those who would like to hasten the discovery and delivery of germline genome editing therapies. Scientists and clinicians must be able to make sense of the legal frameworks within which they operate to carry out their work confidently and responsibly.

In streamlining and modernizing their regulatory frameworks, national lawmakers and regulators should, at a minimum, focus on the research pipeline segments that need the most attention (research with gametes, genome manipulation of embryos, and clinical research) and improve the transparency of applicable laws and regulations. Besides the immediate benefit of a better national regulatory framework, reform initiatives would also have an indirect benefit: they might lead to a wider discussion, beyond the small circle of cognoscenti, engaging lawmakers and hopefully citizens on a high stakes issue. Indeed, an accusation often

157. *See, e.g.,* In Vitro Embryo Research Law of May 11, 2003 (Belg.); B.O.E. 2007, 159, art. 74 (Spain); Jesús & Arellano, *supra* note 84.

158. Jesús & Arellano, *supra* note 84, at 143-44.

159. HUMAN GERMLINE GENOME MODIFICATION AND THE RIGHT TO SCIENCE, *supra* note 2, at 157.

160. Molteni, *supra* note 141.

leveled against current regulatory approaches to the regulation of HGGM is that they are not the outcome of public consultations and deliberations.[161] Considering most legal instruments were adopted in the late 1990s to early-to-mid 2000s, well before the advent of CRISPR, they definitely are not suitable to regulate research and applications of new technology, such as CRISPR. Processes of legal reform might be a twofer: producing modern and coherent regulatory frameworks and engaging the public in an important conversation. National frameworks and experiences will be key in the development of international and transnational governance of human genome editing, but only if necessary legal reforms are made.

161. Sheila Jasanoff et al., *Democratic Governance of Human Germline Genome Editing*, 2 CRISPR J. 266 (2019).