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Medicinal Genome Editing in Germany – Tensions Between Safeguarding and Circumventing Ethical and Legal Standards

BY TIMO FALTUS*

Abstract: Recent breakthroughs in the research and application of genome editing techniques could provide new opportunities for the further development of gene therapy. Irrespective of the achievements already observed and the opportunities that have been predicted so far, there are still questions remaining about the ethical, legal, and regulatory (ELSI) framework for both the research and application of this technology in medicine. This article provides an overview of the legal framework for the medical research and application of genome editing techniques in Germany, considering the legal multi-level system of the European Union (EU) and Germany. This article explains the legal loopholes in current legislation that make the dubious use of genome editing techniques de facto possible, particularly in its medical applications in somatic gene therapy and germline gene therapy. The article also discusses proposals for the further development of the legal framework for using genome editing.

I. INTRODUCTION – WHAT IS SO SPECIAL ABOUT GENOME EDITING TECHNIQUES?

Genome editing methods, unlike other genetic engineering methods such as virus-based transduction methods or chemical transfections, have managed to create interest outside of empirical sciences. In fact, these methods attracted the attention of ELSI researchers, as well as the

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attention of the public.¹ Why is that? The methods in question, which mainly include CRISPR-Cas, zinc-finger nucleases (ZFNs), and transcription activator-like effector nucleases (TALENs), have been explored for decades.² Though they each have a naturally occurring origin, these methods have long stayed under the perceptual radar of ELSI research and the public. This perception started to shift about nine years ago, mainly due to the application-based breakthrough (i.e., the transfer of basic research into practical applications of daily life), especially in relation to the CRISPR-Cas method. The main catalyst for this seems to be that, with the now perfected editing methods, human DNA can be altered in a way that is faster, easier, cheaper, and more accurate than what was previously possible with past methods of genetic engineering. At first glance, these innovations highlight the use of genome editing in human medicine, and the potential they have to possibly improve gene therapy approaches. Therefore, it is not surprising that scientists are swiftly pushing genome editing forward to help further the development of somatic gene therapy.³ It is also not surprising that the age-old debate surrounding the moral status of targeted germline alterations has been rekindled due to these recent innovations in genome editing.⁴ Several parties have already demanded a moratorium, effectively asking that targeted germline alterations not be carried out for the time being.⁵ Generally speaking, as

1. Heidi C. Howard et al., *One Small Edit for Humans, One Giant Edit for Humankind? Points and Questions to Consider for a Responsible Way Forward for Gene Editing in Humans*, 26 EUR. J. HUM. GENETICS 1, 1 (2018); Ana Nordberg et al., *Cutting Edges and Weaving Threads in the Gene Editing (Æ)evolution: Reconciling Scientific Progress with Legal, Ethical, and Social Concerns*, 5 J. L. AND BIOSCIENCES 35, 36 (2018).

2. See Dana Carroll, *Genome Editing: Past, Present, and Future*, 90 YALE J. BIOLOGY AND MED. 653 (2017); Almudena Fernández et al., *A History of Genome Editing in Mammals*, 28 MAMMALIAN GENOME 237 (2017); Puping Liang et al., *Developmental History and Application of CRISPR in Human Disease*, 19 J. GENE MED. 6 (2017).

3. See Daniel P. Dever & Matthew H. Porteus, *The Changing Landscape of Gene Editing in Hematopoietic Stem Cells: A Step Towards Cas9 Clinical Translation*, 24 CURRENT OP. HEMATOLOGY 481 (2017); Simone A. Haas, Viviane Dettmer, Toni Cathomen, *Therapeutic Genome Editing with Engineered Nucleases*, 37 HÄMOSTASEOLOGIE 45 (2017); Nataša Savić & Gerald Schwank, *Advances in Therapeutic CRISPR/Cas9 Genome Editing*, 168 TRANSLATIONAL RES. 15 (2016).

4. For a recent overview of the international debate on the interaction of germline gene modification and the right to science, see Andrea Boggio, Bartha M. Knoppers, Jessica Almqvist, & Cesare Romano, *The Human Right to Science and the Regulation of Human Germline Engineering*, 2 CRISPR J. 134 (2019); 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., 2019).

5. Stephan Guttinger, *Trust in Science: CRISPR-Cas9 and the Ban on Human Germline Editing*, 24 SCI. AND ENG'G ETHICS 1077, 1083 (2018); Eric Lander et al., *Adopt a Moratorium on Heritable Genome Editing*, 567 NATURE 165 (2019); Carrie D. Wolinetz & Francis S. Collins, *NIH Pro Germline Editing Moratorium*, 567 NATURE 175 (2019). See also Edward Lanphier et al.,

genome editing techniques have seen a faster development than the associated ethical and regulatory evaluation of said techniques, the practical implementation of this technology raises questions about its ethical, legal, and social impact. In this respect, the medico-ethical issues surrounding this technology concern the justifiability of using or foregoing this technique in medicine, and the legal issues concern whether the current regulations of genetic engineering in medicine adequately reflect the use of this technology in view of its benefits and risks to individuals and society. It must also be clarified to what extent legal loopholes may make it possible to circumvent existing legal provisions aimed at ensuring the quality and safety of therapies.

II. THE SIGNIFICANCE OF SCIENTIFIC-TECHNICAL DETAILS FOR LEGAL ANALYSIS

The technical character and the technical details of genome editing are usually overrated in the medico-ethical and legal assessment of therapeutic genome editing. When addressing the ethical and legal issues related to the medical research and application of genome editing, the detailed molecular genetic mechanisms are often disregarded. For the legal consideration, all that matters are the editing methods and their consequences, without having to give a detailed description of which molecules of the editing tools will interact with which molecules of the target DNA. Even in the case of other genetic therapy methods, the mode of action at the level of individual atomic bonds and molecular bonds in the DNA is not examined in relation to genetic engineering legislation or pharmaceutical legislation. Instead, the possibility of changing the information content of the DNA that is, or is supposed to be, affected by the respective method is examined; or reference is made to the effect on the DNA brought about by the specific method, usually in the form of a change in the linear sequence of the bases of the DNA. Thus, nothing else can apply for the medico-ethical and legal assessment and handling of genome editing. Rather, genome editing methods must be assessed in the same way as other genetic therapy methods to allow for a comparable legal assessment. In addition, there are no reasons why the therapeutic effects of genome editing should be treated differently than other already established genetic engineering methods in terms of medical ethics or law.

That means in summary: in the context of the ethical, legal considerations of the medical application of genome editing, molecular genetic instructions or descriptions of the mode of action are not necessary. For example, in the ethical, legal analysis of the well-known painkiller acetylsalicylic acid, nobody would describe the molecular mode of action in detail simply to describe the ethics of this painkiller. The medico-ethical and legal analysis is instead based on the benefit-risk ratio of the use of this substance and not on the molecular mode of action (e.g., benefit: pain relief, risk: nausea, vomiting, diarrhea, and micro-bleeding in the digestive tract). Therefore, as with all other therapeutic agents, the ethical and legal evaluation of the methods of genome editing is per se based on (statistically proven) benefit-risk studies, but not on the molecular genetic mode of action.

III. THE MULTILEVEL MATRIX OF THE STATUTORY PROVISIONS OF GENOME EDITING

Six different classes emerge for answering the medico-ethical and legal framework of genome editing in medicine (see Table 1). This is achieved by distinguishing between a) using somatic cells or germline cells, b) doing basic research (e.g., non-therapeutic research using cells and animals) or preclinical research (e.g., therapy orientated research using cells and animals), and c) performing clinical research/studies (e.g., therapy orientated research on humans) or therapy application after market authorization (e.g., routine use). The classes are the following: (1) non-clinical research using somatic human cells⁶ (2) non-clinical research using human germline cells, germ cells and embryos, (3) clinical research on somatic gene therapy, (4) clinical research on germline therapy, (5) routine therapeutic application of somatic gene therapy, and (6) routine therapeutic application of germline therapy.

6. Non-clinical as grouping of basic research and preclinical research. This grouping is useful because the legal frameworks are similar. The main difference between the two is that preclinical research also has to comply with the legally standardized requirements of the Good Laboratory Practice (GLP), which do not apply to basic research.

Table 1: matrix of the statutory regulation of medical genome editing in Germany		
<p>non-clinical research¹ somatic</p> <p>Genetic Engineering Act (Good Laboratory Practice)</p> <p>①</p>	<p>clinical research somatic</p> <p>Directive 2001/20/EC Regulation (EU)² No. 536/2014 Medicinal Products Act</p> <p>③</p>	<p>therapy application somatic</p> <p>Regulation (EC)³ No. 1394/2007 Regulation (EC) No. 726/2004 Medicinal Products Act</p> <p>⑤</p>
<p>non-clinical research¹ germline relevant</p> <p>Embryo Protection Act Genetic Engineering Act (Good Laboratory Practice)</p> <p>②</p>	<p>clinical research germline relevant</p> <p>Embryo Protection Act Directive 2001/20/EC Regulation (EU) No. 536/2014</p> <p>④</p>	<p>therapy application germline relevant</p> <p>Embryo Protection Act Medicinal Products Act Criminal Code</p> <p>⑥</p>
<p>Table Footnotes:</p> <p>1 grouping of basic research and preclinical research</p> <p>2 EU: European Union</p> <p>3 EC: European Community</p>		

The key legal provisions that cover these six areas can be found in German law and EU law. Within German law, the Genetic Engineering Act (GEA),⁷ the Embryo Protection Act (EPA)⁸ and the Medicinal Products

7. Gentechnikgesetz [GenTG] [Genetic Engineering Act], Dec. 16, 1993, BGBl I at 2066, last amended by Verordnung [V], June 19, 2020, BGBl I at 1328, art. 95 (Ger.), <http://www.gesetze-im-internet.de/gentg/BJNR110800990.html>.

8. Embryonenschutzgesetz [ESchG] [Embryo Protection Act], Dec. 19, 1990, BGBl I at 2746, last amended by Gesetz [G], Nov. 21, 2011, BGBl I at 2228, art. 1 (Ger.), <http://www.gesetze-im-internet.de/eschg/BJNR027460990.html>.

Act (MPA)⁹ are of primary importance. When it comes to EU legislation, the pharmaceutical directive (Directive 2001/83/EC),¹⁰ the advanced therapy medicinal products (ATMP) regulation (Regulation (EC) No. 1394/2007)¹¹ and the regulation on the marketing of medicinal products (Regulation (EC) No. 726/2004)¹² must be considered. It is worth noting that Directive 2001/20/EC still applies in the EU for the legal management of clinical studies.¹³ However, this directive will most likely be replaced in 2021 or 2022 by the already published Regulation (EU) No. 536/2014.¹⁴ It is also worth noting that EU regulations are directly applicable to all member states of the EU, which includes Germany. In contrast, EU directives are addressed first and foremost by the legislators of the member states, who have to transpose the provisions of the directives into national provisions for the harmonization of national laws. In this case, although the respective national provisions dictate the law, these will also contain provisions of EU law. The provisions referred to here, and that can be seen in Table 1, are only the essential provisions governing prohibitions and approval requirements for genome editing in human medicine. Table 1 does not offer a detailed description of the general legislation that regulates informed consent, regardless of the medical procedures used or data protection issues and ownership of donated cells.

A. Non-Clinical Research on Somatic Cells ①

In Germany, the use of genome editing methods on somatic cells is neither a priority nor explicitly prohibited. Therefore, it is legally permissible to use genome editing methods, on the condition that general legal provisions such as provisions concerning workplace and laboratory safety are observed. As with the other classes, genetic engineering

9. Arzneimittelgesetz [AMG] [Medicinal Products Act], Dec. 12, 2005, BGBl I at 1869, last amended by Gesetz [G], Dec. 9, 2020, BGBl I at 2870 (Ger.), http://www.gesetze-im-internet.de/amg_1976/BJNR024480976.html.

10. Council Directive 2001/83, of the European Parliament and of the Council of 6 November 2001 on the Community Code relating to Medicinal Products for Human Use.

11. Regulation (EC) 1394/2007, of the European Parliament and of the Council of 13 November 2007 on Advanced Therapy Medicinal Products and Amending Directive 2001/83/EC and Regulation (EC) 726/2004.

12. Council Regulation (EC) 726/2004, of the European Parliament and of the Council of 31 March 2004 laying down Community Procedures for the Authorisation and Supervision of Medicinal Products for Human and Veterinary Use and Establishing a European Medicines Agency.

13. Council Directive 2001/20/EC, of the European Parliament and of the 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.

14. Regulation (EU) 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.

laboratory activities must comply with the GEA provisions on the operation of genetic engineering laboratories.¹⁵ Legal questions in non-clinical research on the genetic modification of somatic cells using genome editing methods do not differ from legal questions in non-clinical research on the genetic modification of human cells using methods other than genome editing. In summary, the non-clinical use of human cells in combination with genome editing primarily involves questions of informed consent regarding cell donation and the use of the cells, data protection issues relating to genetic information gained from the donated cells, and questions of civil property rights regarding the donated cells. Reference may be made to the previous discussion on basic research and preclinical research with somatic human cells.¹⁶ The current provisions in this area appear to cover genome editing adequately. Since the use of somatic human cells in genome editing research raises no new questions, this class can be regarded as medico-ethically and legally unproblematic.

B. Non-Clinical Research on Germline Cells, Germ Cells and Embryos ②

Targeted germline alterations on germline cells and germ cells are explicitly prohibited by the EPA in Germany;¹⁷ this ban applies to all methods and all objectives. Both genetic alterations, which are directed towards the therapy of hereditary diseases and interventions for enhancement (improvement of human characteristics without reference to a disease), are covered and thus prohibited. The prohibition in the 1990 EPA already existed before genome editing came about.¹⁸ However, according to EPA Section 5.4 No. 1 and 2, using germline cells and germ cells for the scientific purpose of intentionally altering their genetic characteristics is permissible under certain conditions. This research is permissible if the researchers ensure that the genetically modified germ cells are not used for fertilization, that the altered germline cells are not transferred to an embryo, fetus, or human, or that no germ cells arise from them.

15. Genetic Engineering Act §§ 7-12.

16. Hannah B. Baker, John P. McQuilling & Nancy M. P. King, *Ethical Considerations in Tissue Engineering Research: Case Studies in Translation*, 99 *METHODS* 135, 137 (2016); ERWIN DEUTSCH & ANDREAS SPICKHOFF, *MEDIZINRECHT, ARZTRECHT, ARZNEIMITTELRECHT, MEDIZINPRODUKTERECHT UND TRANSFUSIONSRECHT* 805 (7th ed. 2014); Rob B.M. de Vries et al., *Ethical Aspects of Tissue Engineering: A Review*, 14 *TISSUE ENG'G: PART B* 367, 370 (2008). See Rina Hakiman & David Korn, *Ownership and Use of Tissue Specimens for Research*, 292 *JAMA* 2500 (2004).

17. Embryo Protection Act § 5(1).

18. *Id.*

Even so, advancing technologies have made it possible to circumvent these prohibitions.¹⁹ For such germline alterations, genome editing methods as well as other methods for DNA modification can be used. These methods must then be combined with other biotechnological and genetic engineering techniques to first produce oocytes and sperm cells that are not covered by the provisions of the EPA. The oocytes and sperm cells are not naturally derived from germline cells. Instead, they are derived extracorporeally by methods of stem cell biology either from biopsied adult stem cells or from initially biopsied somatic cells, which are then transformed into induced pluripotent stem cells (iPS cells).²⁰ The production of oocytes and sperm from stem cells is not covered by the EPA, neither for research purposes nor for therapeutic purposes, and therefore is not prohibited. The non-applicability of the EPA to artificially derived oocytes and sperm cells is justified by the fact that the EPA's definition of germ cells (in EPA Section 8.3) is linked to a medical formation process explicitly described in the EPA: "For the purposes of this Act, germ line cells are all cells that lead in a cell line from the fertilised egg to the egg and sperm cells of the human being resulting from this fertilised egg. . .". In accordance with EPA Section 8.3, germ cells must originate from germline cells. Therefore, according to the EPA, germ line cells or germ cells can only be cells that originate from a (continuous) cell line, in other words, from the fertilized egg to the oocytes and the sperm cells of the human being that have also arisen from the fertilized egg. In addition, the oocyte may be a germline cell within the meaning of the EPA from the moment of sperm cell insertion or penetration until fertilization is completed with nuclear fusion.. Thus, the EPA has linked its legal definition of germline cells and germ cells to a specific development process and not to a functional description independent of the development process. In any case, this process, which is required by law, does not exist in both germline cells and germ cells produced from stem cells, other than the primordial germ cells in the germline. The law

19. See Timo Faltus & Ronny Schulz, *Die arzneimittelrechtliche Handhabung zellbasierter Therapien in Point-of-Care-Behandlungsmodellen*, 37 PHARMR 228 (2015); see also Timo Faltus, *Rechtsrahmen der Eigenfettnutzung bei Point-of-Care-Behandlungen in der plastischen und ästhetischen Chirurgie - Straf- und berufsrechtliche Risiken aufgrund des Arzneimittelrechts*, 48 HANDCHIRURGIE MIKROCHIRURGI PLASTISCHE CHIRURGIE 219 (2016) [hereinafter *Rechtsrahmen der Eigenfettnutzung* bei].

20. Saskia Hendriks et al., *Artificial Gametes: A Systematic Review of Biological Progress Towards Clinical Application*, 21 HUM. REPROD. UPDATE 285 (2015); Javad Amini Mahabadi et al., *Derivation of Male Germ Cells from Induced Pluripotent Stem Cells by Inducers: A Review*, 20 CYTOTHERAPY 279 (2018); Immaculda Moreno et al., *Artificial Gametes from Stem Cells*, 42 CLINICAL AND EXPERIMENTAL REPROD. MED. 33 (2015).

would need to be amended to change the description of germ cells to a function-based model in order to account for artificially produced germline cells and germ cells in the scope of the EPA, as well as make corresponding prohibitions—such as sections 5.1 and 5.2 of the EPA—legally binding for artificially produced germline cells.²¹ However, prior to any amendment of section 8.3 of the EPA, the current legal requirements still apply (i.e., a) the statutory prohibitions of the EPA regarding germline changes (in section 5), which refer only to naturally occurring germline cells and germ cells because of the link to the EPA's definition of germ cells in section 8.3 of EPA, and b) the current legal requirements must not be applied to artificially produced germline cells or germ cells.). This non-applicability of the EPA stems also from the constitutional ban on using analogies to the detriment of the acting person (Art. 103.2 of the German Basic Law which serves as the German Constitution). According to this constitutional provision, only such action may be punished which was prohibited by law before the action (general rule: *nulla poena sine lege stricta*). The application of the prohibition on the therapeutic use of genetically modified germ cells with respect to artificially produced germ cells would only be possible if the relevant prohibition of the EPA could be applied by analogy. This is due to the fact that in this case only the meaning (i.e., artificial intervention into the germ line) of the described criminal provision would be decisive for its application. However, this application would go beyond the literal sense of the provision (i.e., naturally arising gametes). Although, as shown, such an analogous application is prohibited.

Finally, for the inclusion of artificially produced germ cells or germline cells in the scope of the EPA, the argument does not apply that artificially produced germline cells and germ cells must be covered by the EPA or else the resulting embryo or later born human would not have originated from germ cells. This argument confuses the legal/policy field with the scientific/empirical field. There is neither a lawful nor a non-lawful reason why these two fields must be congruent in content. There are no reasons why the actual (and legal) existence of a born human being must necessarily be bound to the legal existence of germ cells. Due to a lack of legal prohibitions, artificially produced germline cells and germ cells can be used to a legally permissible extent even beyond what is permissible with naturally occurring germline cells or germ cells. On the one hand, artificially produced germline cells and germ cells could be legally

21. TIMO FALTUS, STAMMZELLENREPROGRAMMIERUNG - DER RECHTLICHE STATUS UND DIE RECHTLICHE HANDHABUNG SOWIE DIE RECHTSSYSTEMATISCHE BEDEUTUNG REPROGRAMMIERTER STAMMZELLEN 392, 459 (2016).

genetically modified. On the other hand, in contrast to naturally occurring germline cells or germ cells after their genetic modification, these edited cells could also be transferred to an embryo or to humans. Genetically modified germ cells could even be used for fertilization purposes. If this contradiction is to be eliminated, then this can only be done by an amendment to the law as described above.

Germline genetic changes of embryos for research on genome editing are also prohibited by the EPA.²² With regard to the use of genome editing procedures in extracorporeal embryos, there are several legal loopholes as a result of the time discrepancy between technical progress and the resilience of required legislative amendments. In addition, these loopholes also arise from the above-mentioned prohibition of the use of analogous criminal prohibitions, which makes possible the use of genome editing in extracorporeal embryos which were not recognized by the legislators when the EPA was enacted.

For embryos that are sexually derived from naturally occurring germ cells (i.e., germ cells within the meaning of the EPA as described above), the prohibition of germline manipulation is safeguarded in two respects. Single-cell embryos (i.e., fertilized egg cell) and totipotent cells in a multicellular embryo are also considered germline cells (EPA Section 8.3), meaning that artificial changes of their genetics would constitute a forbidden germline change according to section 5.1 of the EPA. It is further prohibited under section 2.1 of the EPA to use an extracorporeally created embryo for purposes other than the preservation of the embryo. The experimental use of editing methods on embryos does not serve to preserve these embryos, which means that corresponding actions are prohibited and can be punished with imprisonment of up to three years or with a fine under section 2.1 of the EPA. The relationship between EPA Sections 5.1 2.1 leads to unsolved legal problems in the case of targeted alterations of the germline of embryos for the treatment of the genetic basis of a hereditary disease. Such a genetic alteration could possibly be compatible with Section 2.1 of the EPA,²³ but such an alteration would always be prohibited by section 5.1 of the EPA. Therefore, if the causal therapy of hereditary diseases in the embryo is to be legally permissible in the future, these two provisions would have to be aligned with each other by amending the EPA.

However, the prohibitions of the misuse of embryos described above only apply if the embryo entities in question are considered

22. Embryo Protection Act § 5.

23. "Anyone who uses an extracorporeally created embryo for a purpose that does not serve its preservation will be punished."

embryos under the EPA. In that regard, similar to the use of artificially produced germline cells, there are legal problems relating to bypassing legal prohibitions. The application of genome editing to embryos (in a medical, empirical sense) is permitted in Germany if the entities concerned are not considered embryos under the EPA. Section 8.1 of the EPA defines what constitutes an embryo. Accordingly, for the purpose of this Act, the meaning of an embryo shall encompass the human egg cell, fertilized and capable of developing, from the time of fusion of the nuclei, as well as any totipotent cell removed from an embryo that is capable of dividing and developing into an individual under appropriate conditions. This legal definition thus refers to the sexual origin of an embryo, and states that, the entities in question also have to be able to develop. Asexually derived entities, such as embryos from somatic cell nucleus transfer (Dolly method) or “synthetic human entities with embryo-like features” (SHEEFs),²⁴ are not considered embryos under the EPA by the majority of legal scholars.²⁵ In contrast to sexually created embryos, genome editing studies could be carried out on such asexually derived embryos if they were produced with human cells. If this contradiction is to be eliminated, it can only be done by an amendment to the EPA.

It is disputed in Germany whether sexually *and* asexually produced embryos may be used for research on germline alterations if they are embryos that are inhibited in their development in such a way that no born human can arise from them. If such embryos are entities that were derived asexually (i.e., without fusion of oocyte and sperm cell), then, as described above, one must assume that such entities are not covered by the prohibitions of the EPA. It becomes more complex when trippronuclear embryos (3PN zygotes) are involved, which have already been genetically modified outside Germany with genome editing methods.²⁶ In principle, these 3PN zygotes are sexually derived embryos, so they are covered by the legal embryo definition within the EPA. Consequently, prohibitions regarding the misuse of embryos and the prohibition of germline alteration must be taken into account. Only when a 3PN zygote (as well as all other sexually created embryos) stops its further development on its own (i.e., showing no more cell divisions), will the respective

24. See John Aach et al., *Addressing the Ethical Issues Raised by Synthetic Human Entities with Embryo-like Features*, ELIFE, Mar. 21, 2017, at 1, File No. e20674.

25. For a list of further references with different views, see FALTUS, *supra* note 21, at 374-83, 387-93.

26. For genome editing advances in China using 3PN zygotes, see Puding Liang et al., *CRISPR/Cas9-Mediated Gene Editing in Human Trippronuclear Zygotes*, 6 PROTEIN CELL 363 (2015) and Changyang Zhou et al., *Highly Efficient Base Editing in Human Trippronuclear Zygotes*, 8 PROTEIN CELL 772 (2017).

3PN zygote no longer be considered an embryo under the EPA. A prospective assessment of the developmental stop, even if it is sure to occur, does not legally justify the use of that embryo for research purposes. Provided that new research possibilities are to be created in a legally secure manner, the existing legal definition of embryos in section 8.1 of the EPA with regard to the embryo's development capacity would have to be amended from the abstract, open-ended wording to a wording with a specific development stage. This specific wording would have to name a certain state of development (e.g., formation of the neural tube). If, on the basis of empirical observations, it was established that certain embryos could not reach a specific, legally definable stage of development in specific situations, then these embryos could possibly be used for research purposes. From an ethical point of view, this would also entail that the developmental phases prior to this specific state are not worthy of moral protection (like born human beings are).

Another discussion concerns the legal status of embryos created in vitro from artificially created germ cells. If two artificially produced germ cells (i.e., egg cell and sperm cell) are used, then the process of embryo generation is indeed sexual, which in principle means that an embryo as defined by the EPA may be present. The problem with this is that, as mentioned above, such artificially generated germ cells are not germ cells in the sense of the law. The unresolved question arises as to whether an embryo within the meaning of the EPA can develop from germ cells, which are not germ cells under this Act. These questions become even more complex if one of the germ cells is naturally developed, but the other germ cell is artificially produced. So far, these are merely academic considerations, as the practical implementation does not (yet) seem to be technically mature and because physicians and scientists concerned are certainly also deterred by the legal situation from attempting it. These academic questions about the legal status of embryos, which are based on the use of artificially produced germ cells, would dissolve only at the moment when the embryos in question would have been transferred to a woman and have implanted in the uterus. This is because the EPA is no longer applicable once an embryo is implanted in the uterus. Instead, the German Criminal Code's provisions on abortion is relevant (Section 218-2019b). The Criminal Code does not refer to the creation of an embryo, and the Criminal Code does not even use the term "embryo," only referring to "nidation" and "pregnancy."²⁷ Put simply, a pregnancy under the

27. See generally Strafgesetzbuch [StGB] [German Criminal Code], last amended by Gesetz [G], Mar. 30, 2021, BGBl I. 844, art. 1, <https://www.gesetze-im-internet.de/stgb/> (Ger.) (using "nidation" and "pregnancy" multiple times throughout the Code).

Criminal Code occurs as soon as an embryo is implanted in the uterus.²⁸ Based on this general formulation, all embryos, regardless of their technical origin, would be covered by the Criminal Code.

C. Clinical Research on Somatic Gene Therapy ③

For clinical research on somatic gene therapy, both with and without genome editing, the same criteria for clinical research on other therapies apply, requiring statistically proven efficacy, safety, and quality. For subsequent market approval, a benefit/risk assessment appropriate to the particular clinical picture and the patient group should be carried out in clinical trials. Clinical trials are standardized by law in the EU and in Germany. The respective provisions can currently still be found in the EU Directive 2001/20/EC. In Germany, the provisions from this EU Directive are contained in the German Medicinal Products Act as well as in the German Good Clinical Practice Executive Order. It is anticipated that from 2020 the existing provisions of the EU Directive will be replaced by the already published EU Regulation No. 536/2014.

In relation to medical ethics and the legal requirements for carrying out a clinical trial, the following general provisions must be observed as in any other gene therapy clinical trial: in accordance with the provisions of pharmaceutical legislation, a clinical trial may only be conducted if approval from the responsible ethics committee and approval from the competent medicinal products authority have been obtained. The ethics committee must weigh the benefit of the study against a potential risk to the participants. It also verifies that the medical facilities where the study will take place are appropriate and that their medical staff has the necessary qualifications and experience for the study. The ethics committee also checks whether the written explanations on informed consent are comprehensible for the participants of the study and whether the participants' written declarations of consent are complete. Only when these conditions are met will the ethics committee give its consent to carry out the study. In addition, it is required that the competent medicinal products authority has positively evaluated the clinical trial from a medical point of view.

D. Clinical Research with Targeted Germline Alteration ④

In clinical research on targeted germline gene alteration, four categories must be distinguished: a) clinical studies with born humans, b) clinical studies using edited germ cells and generation of respective

28. See German Criminal Code (Ger.), § 218, para. 1.

edited embryos, c) editing alterations on an embryo in utero, and d) genome-editing alterations on an embryo in vitro with subsequent transfer of the edited embryo. In the case of born humans, clinical studies that lead to a change in the genetic germline identity of the participant may not be performed in accordance with the currently applicable EU Directive 2001/20/EC²⁹ or in accordance with EU Regulation No. 536/2014.³⁰ Whether the targeted germline editing is additionally prohibited by the German EPA is disputed, as the provisions of the EPA and its prohibitions on targeted germline manipulation were enacted to regulate the manipulation of germline cells and germ cells in vitro. Whether these provisions also apply to born humans seems questionable. At least with regard to born humans, in the case of germline altering interventions, it is always necessary to consider the general bans on bodily harm of the German Criminal Code. (see Part F).

There are no independent legal provisions that regulate or explicitly prohibit germline-altering interventions on an embryo in utero. Whether the provisions of the EPA are applicable is also disputed since this law was not adopted for the regulation of handling embryos in vivo/in utero. The provisions on abortion from the Criminal Code should be considered, however. For example, if the germline alteration of the embryo in utero would cause the abortion and this would not be in accordance with the consent of the mother, it could be a prohibited and punishable abortion.³¹ Regarding embryos in utero, it is also questionable whether the prohibitions under the mentioned EU law should be observed in the conduct of clinical studies leading to a change in the participant's genetic germline identity. It is unclear whether these rules are also applicable to embryos (whether in utero or in vitro). Applicability requires that embryos would be regarded as study participants; in other words, embryos would have to be treated, in legal terms, as born human beings as the wording of these EU acts refers to study participants.³²

In contrast, clinical research on germline-relevant alterations on embryos in vitro is explicitly prohibited by the EPA, and possibly by regulations governing clinical trials. Although genome editing is not explicitly mentioned in the provisions of the EPA, the corresponding procedures are nevertheless covered since Section 5.1 of the EPA

29. Directive 2001/20/EC, *supra* note 13, art. 9.6.

30. Regulation (EU) 536/2014, *supra* note 14, art. 90.

31. German Criminal Code (Ger.), § 218, para. 2, sentence 1.

32. Timo Faltus, *No Patent-No Therapy: A Matter of Moral and Legal Consistency Within the European Union Regarding the use of Human Embryonic Stem Cells*, 23 STEM CELLS AND DEV. 56, 58 (2014); FALTUS, *supra* note 21, at 730-39.

generally prohibits the artificial alteration of the genetic information of human germline cells and germ cells. The ban is ethically justified since its adoption, *inter alia*, by the argument that germline therapy methods cannot be developed without previous experiments on humans. However, such studies would not be justifiable because of the potentially irreversible consequences in the experimental phase (failures with non-excludable genetic damages to the participant).³³ In addition, as for non-clinical research, it should be noted that the use of human embryos for research purposes is prohibited in Germany without exception under Section 2.1 of the EPA. One must keep in mind that there are the above mentioned and yet unanswered questions as to whether the EU's prohibitions of clinical trials involving gene therapies that lead to an altered genetic germline identity of the trial participant can also be applied to embryos. The statements made under Part B apply with regard to the legal issues, in particular with regard to the technical possibilities for circumventing the legal prohibitions on the use of edited germ cells in clinical trials.

E. Somatic Therapy Application of Genome Editing ⑤

Therapeutics based on genome editing are, in legal terms, usually gene therapeutics. This assessment is based on article 2.1 of the ATMP Regulation in conjunction with part one of annex one to Directive 2001/83/EC. Accordingly, a gene therapeutic is to be understood as a biological medicinal product with the following characteristics:

(a) it contains an active substance which contains or consists of a recombinant nucleic acid used in or administered to human beings with a view to regulating, repairing, replacing, adding or deleting a genetic sequence; (b) its therapeutic, prophylactic or diagnostic effect relates directly to the recombinant nucleic acid sequence it contains, or to the product of genetic expression of this sequence.³⁴

Yet the multitude of therapeutic uses of genome editing procedures do not allow for a general classification of these methods as gene therapeutics. For this purpose, rather, a case-by-case assessment with regard to the respective therapeutic is necessary. If, in some cases, the therapeutic in question is not a gene therapeutic, it must be examined whether this

33. Hubert Schorle & Frank Tüttelmann, "Gene-Editing"-Verfahren - Stellungnahme der DVR-Mitglieder AAD, ADI, AGRBM, DGA, DGGEF, D.I.R, SRBM und SEF unter Federführung der DGRM, 13 JOURNAL FÜR REPRODUKTIONSMEDIZIN UND ENDOKRINOLOGIE 18 (2016); Gesetzentwurf der Bundesregierung [Bill of the Federal Government], Bundestagsdrucksache [Printed Matters of the German Federal Parliament] 11/5460, at 11, <http://www.dip21.bundestag.de/dip21/btd/11/054/1105460.pdf> (Ger.).

34. Directive 2001/83, *supra* note 10, art. 2.1.

therapeutic, which is using genome editing, is a somatic cell therapy in accordance with article 2.1.a of the ATMP Regulation and part four of annex one of Directive 2001/83/EC, or whether the therapeutic is a biotechnologically processed tissue product in accordance with articles 2.1.a and 2.1.b of the ATMP Regulation. Legally speaking, not every genetically engineered cell or derived therapeutic will automatically be considered gene therapy, even if there are detectable genetic changes in the therapeutic cells. Instead, they might be considered genetically engineered cells within one of the two latter classes of medicinal products.³⁵

In the EU, ATMP manufacturing requires that a manufacturing license be issued by local pharmaceuticals authorities.³⁶ Manufacturing must then take place under Good Manufacturing Practice (GMP) conditions (article 5 of the ATMP Regulation). ATMP may only be placed on the market in the EU after official market approval per articles 27 and 28 of the ATMP Regulation, and article 3 of Regulation (EC) No. 726/2004. Thus, the regular therapy application of such therapeutics is possible only after market approval. Among other things, the granting of approval requires that the therapeutic in question has been successfully tested in a preclinical and clinical environment. Regarding the regulatory management of the therapeutic application of genome editing, however, the questions of the legal, and thus ethical, requirements of the corresponding clinical studies or market approval are often addressed too quickly. Such considerations overlook current technological developments in the field of therapeutic application of cell-based therapeutics, and more specifically, in the application of genome editing. Legal issues of clinical trials and the market approval of medicinal products only arise when the medicinal product in question is placed on the market in legal terms. Both EU law and the German Medicinal Products Act explicitly refer to the act of placing them on the market.³⁷ It follows that a medicinal product that is not legally placed on the market is not subject to market authorization and can therefore be used without it. For some time now, technological advances in the fields of ATMP production and use have made it possible to offer ATMP that are not placed on the market in legal terms. This would be the case in particular when the therapeutic is manufactured by a physician, then applied to his patient by the physician or under the supervision of the physician that manufactured the pharmaceutical. From a

35. Brigitte Anliker et al., *Genetisch modifizierte Zellen zur Therapie verschiedener Erkrankungen* 58 BUNDGESUNDHEITSBL 1274 (2015).

36. Regulation (EC) 1394/2007, *supra* note 11, art. 5.

37. Cf. Directive 2001/83/EC, *supra* note 10, art. 2.1; Regulation (EC) 726/2004, *supra* note 12, art. 3.1; Regulation (EC) No. 726/2004; Medicinal Products Act § 1.

legal point of view, for example in Germany, this procedure is not considered placement on the market, since placement on the market presupposes a transfer of power of disposition of the therapeutic. Yet if a physician personally manufactures a medicinal product and applies it to a patient, the patient cannot then dispose of the medicinal product to another person.

In recent years, technological advances have made it possible to quickly develop technical devices that allow the manufacturing and application of gene therapeutics at the point-of-care. Such technical devices are already available to physicians, and corresponding medical literature is available regarding the usage of this technique.³⁸ The manufacture and use of somatic gene therapeutics based on genome editing can also be carried out without placing them on the market. After all, the scientific discourse regularly emphasizes the technical simplifications offered by genome editing methods for the targeted generation of very specific genetic modifications. As a result of this simplification, it is possible that a significant portion of somatic gene therapeutics may not legally require clinical trials or market approval. Nevertheless, they may still be used in therapy. The regulatory discussion on the medical and legal handling of the editing methods should therefore also include the growing sector of in-house medicinal product manufacturing and should begin to develop a regulatory approach to control and ensure quality, safety, and efficacy of therapeutics. However, from a medico-ethical point of view, this development is questionable because physicians' privileged regulatory approach to manufacturing of medicinal products may become the factual norm. Even so, the regular use of a medicinal product requires, among other things, a statistically verified development in preclinical and clinical studies in order to guarantee a certain level of safety.

Today, a general prohibition from the Medicinal Products Act is available to prevent such clinically unproven therapies. In accordance with section 5 of the MPA, placement on the market or the use of unsafe medicinal products on another human is prohibited. Medicinal products are considered unsafe if, according to the current level of scientific knowledge, there is a sufficient reason to suspect that when used in accordance with their intended purpose they have harmful effects that

38. See Jennifer E Adair et al., *A Point-of-Care Platform for Hematopoietic Stem Cell Gene Therapy*, 126 BLOOD 4416 (2015) [hereinafter Adair et al., *A Point-of-Care Platform*]. See also Jennifer E Adair et al., *Semi-automated Closed System Manufacturing of Lentivirus Gene-modified Haematopoietic Stem Cells for Gene Therapy*, 7 NATURE COMM'NS, Oct. 2016, at 1 (2016) [hereinafter Adair et al., *Semi-automated Closed System Manufacturing*]. See generally *Opening the Door to Backroom Biologics*, 37 NATURE BIOTECHNOLOGY 1097 (2019).

exceed the tolerable limit in light of current medical knowledge.³⁹ The determination of whether the same logic applies to somatic genetic therapies that are manufactured by physicians depends on a case-by-case evaluation.

If one assumes, concerning somatic cells, that substances for enhancement by means of genetic engineering procedures such as genome editing are also medicinal products in the legal sense, then it is questionable whether an “unknown substance” would be given the necessary authorization to conduct clinical studies solely to investigate purposes of enhancement. It seems questionable whether there is justification for exposing people to the unknown health risks of an undisclosed substance or an unknown treatment method in clinical studies simply to test whether a genetic, physiological, or neurological enhancement may be achieved. Irrespective of the question whether enhancement is a medicinal product in the legal sense, it is always questionable whether enhancement has an effect on the human body that is compatible with criminal law or whether it is (already) a punishable bodily harm (see Part F). More problematic in genetic enhancement are cases of genetic modification carried out on the patient’s own body, which have become possible through technical simplifications in the field of genome editing.⁴⁰ Cases of deliberate self-endangerment are not yet able to be addressed by pharmaceutical or criminal law, and thus, are not regulated by any law, so long as there is no third person endangerment.

F. Therapeutic Germline Application ⑥

As with the questions on the clinical examination of targeted germline alteration, various constellations are also possible when it comes to therapeutic application. The legal handling of these constellations is basically to be evaluated as described under Part D. As for the use of germline therapeutics in born humans, the prohibition relating to unsafe medicinal products (section 5 of the MPA) should be considered as described in Part E, in addition to the aspects mentioned in Part D. Whether such an unsafe medicinal product, whether for the treatment of hereditary diseases or purposes of enhancement, is present in a targeted germline alteration in born humans has yet to be answered. Furthermore, born humans are protected against assault and battery by sections 223, 224, and 226 of the Criminal Code. These general provisions include

39. Medicinal Products Act § 5(2).

40. Eric Smalley, *FDA Warns Public of Dangers of DIY Gene Therapy*, 36 NATURE BIOTECHNOLOGY 119 (2018); *Opening the Door to Backroom Biologics*, *supra* note 38.

protection against targeted and unwanted germline change. However, it is questionable how targeted germline changes that a patient desires will be assessed according to the Criminal Code. Whether such a germline change would satisfy the criminal offense of bodily harm depends on whether the patient consented to such treatment, rendering the change not punishable under section 228 of the Criminal Code, or whether, despite consent, the treatment violates moral standards, rendering such change punishable. How such a germline change would violate moral standards must be clarified—as for the question of unsafe medicinal products per section 5 of the MPA—by the medical field and the ELSI disciplines.

Concerning the therapeutic application of genome editing to germ cells and embryos, the comments made in Part B regarding the complex interplay between sections 5.1 and 2.1 of the EPA, and the comments on Clinical Research with Targeted Germline Alteration in Part D apply. Moreover, the following should be considered: Even if Germany permitted germline therapy under the EPA in sections 2.1 and 5.1 (see Part B), the development of appropriate therapies is unlikely to be legally possible because the conduct of necessary clinical studies in the EU as described in Part D is excluded. Market approval is not possible without clinical studies. In Germany, this legal restriction could be bypassed by using germline therapeutics which are not placed on the market in legal terms, such as therapeutics manufactured and used by physicians in-house. For these germline therapeutics, no clinical studies or market approval is necessary. In addition, there are legal loopholes in the current legislation for the therapeutic application of genome editing, which arise from using artificially produced germ cells from stem cells as described in Part B. Germ cells derived from stem cells do not exist under the EPA, and thus, they can be genetically edited and legally used for therapeutic purposes. As a result of such loopholes in the law, germline therapy prohibited by the legislature could be possible. It is therefore the legislature's task to close this gap by applying the same rules to artificial germ cells as applied to naturally occurring germ cells.

The international moratorium to stop the implementation of germline alterations by genome editing would apply only to cases not already prohibited by German law. However, in Germany, many options for germline therapies are already prohibited by law. Thus, neither a moratorium nor further statutory prohibitions are necessary. Legislators could include cases that are not already covered by the current prohibitions due to technological advances that have occurred since the initial enactment of the relevant laws by amending the existing legislation and expressly

prohibiting the current uncovered cases. This approach would be more legally secure than a moratorium.

IV. OUTLOOK

The application-oriented development of genome editing in medicine is—similar to the previous discovery, research and clinical applicability of iPS cells—important not only for the sciences, medicine and technology, but also for the ELSI disciplines. Just as iPS cells were a catalyst for discussing, among other things, the meaning of iPS cells for the further use of human embryonic stem cells, genome editing is the catalyst for the ELSI disciplines discussing the meaning this technology will have for the further development of genetic medicine. Although genome editing and iPS technology are already merging,⁴¹ ELSI work in these areas is still needed. It remains to be seen if the ELSI questions in these areas will turn out to be nothing more than fictitious giants, which on closer inspection become smaller because the supposed ELSI problems are not so different from previous ELSI assessments of earlier technologies with social implications. Instead, ELSI questions in medical genome editing could be comparable to previous questions researchers dealt with. New ELSI solutions will be necessary only if it turns out that there are completely new questions. In any case, the respective ELSI studies and their recommendations are important for the further development of therapy, so that therapies can be developed that are socially acceptable beyond their technical feasibility.

V. TRANSLATED GERMAN LEGAL ACTS

A. Extract from the Basic Law for the Federal Republic of Germany

Article 103

- (1) In the courts every person shall be entitled to a hearing in accordance with law.
- (2) An act may be punished only if it was defined by a law as a criminal offence before the act was committed.
- (3) No person may be punished for the same act more than once under the general criminal laws.

41. Morgan L. Maeder & Charles A. Gersbach, *Genome-Editing Technologies for Gene and Cell Therapy*, 24 MOLECULAR THERAPY 430, 439 (2016). See Matthew H. Porteus, *Towards a New Era in Medicine: Therapeutic Genome Editing*, 16 GENOME BIOLOGY 286 (2015).

B. Extract from the German Criminal Code

Section 218 - Abortion

- (1) Whoever terminates a pregnancy incurs a penalty of imprisonment for a term not exceeding three years or a fine. Acts whose effects occur before nidation is completed are not deemed to be a termination of pregnancy within the meaning of this statute.
- (2) In especially serious cases, the penalty is imprisonment for a term of between six months and five years. An especially serious case typically occurs where the offender
 1. acts against the will of the pregnant woman or
 2. recklessly places the pregnant woman in danger of death or at risk of serious damage to health.
- (3) If the act is committed by the pregnant woman, the penalty is imprisonment for a term not exceeding one year or a fine.
- (4) The attempt is punishable. The pregnant woman is not liable for attempt.

Section 223 - Bodily harm

- (1) Whoever physically assaults or damages the health of another person incurs a penalty of imprisonment for a term not exceeding five years or a fine.
- (2) The attempt is punishable.

Section 224 - Dangerous bodily harm

- (1) Whoever causes bodily harm
 1. by administering poison or other substances which are harmful to health,
 2. using a weapon or other dangerous implement,
 3. by means of a treacherous assault,
 4. acting jointly with another party to the offence or
 5. using methods which pose a danger to life incurs a penalty of imprisonment for a term of between six months and 10 years, in less serious cases imprisonment for a term of between three months and five years.
- (2) The attempt is punishable.

Section 228 - Consent

Whoever inflicts bodily harm with the victim's consent is only deemed to act unlawfully if, despite that consent, the act offends common decency.

C. Extract from the German Embryo Protection Act

Section 2 - Improper use of human embryos

- (1) Anyone who disposes of, or hands over or acquires or uses for a purpose not serving its preservation, a human embryo produced outside the body, or removed from a woman before the completion of implantation in the uterus, shall be punished with imprisonment of up to three years or a fine.
- (2) Anyone who causes a human embryo to develop further outside the body for any purpose other than to bring about a pregnancy shall be punished likewise.
- (3) Any attempt shall be punishable.

Section 5 - Artificial alteration of human germ line cells

- (1) Anyone who artificially alters the genetic information of a human germ line cell shall be punished with imprisonment of up to five years or a fine.
- (2) The same shall apply to anyone who uses a human germ cell with artificially altered genetic information for the purpose of fertilization
- (3) Any attempt shall be punishable.
- (4) Paragraph 1 shall not apply to
 1. an artificial alteration of the genetic information of a germ cell located outside the body, if any use of it for fertilization has been rule out,
 2. an artificial alteration of the genetic information of a different body germline cell that has been removed from a dead embryo, from a human being or from a deceased person, if it has been ruled out that
 - a. the cell will be transferred to an embryo, fetus or human being, or
 - b. a germ cell will originate from it, as well as
 3. an inoculation, radiation, chemotherapeutic or other treatment by which an alteration of the genetic information of germ line cells is not intended.

Section 8 - Definition

- (1) For the purpose of this Act, an embryo shall already mean the human egg cell, fertilized and capable of developing, from the time of fusion of the nuclei, as well as any totipotent cell removed from an embryo that is capable of dividing and developing into an individual under appropriate conditions.

(2) In the first twenty-four hours after the fusion of nuclei, the fertilized human egg cell is held to be capable of development except if it is established before expiration of this time period that the egg cell will not be capable of developing beyond the one cell stage.

(3) Germ line cells, for the purpose of this Act, shall be any 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.