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Deciphering the Fragmentation of the Human Genome Editing Regulatory Landscape

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Genome editing techniques have generated a growing interest following the discovery of the so-called CRISPR-Cas technique. It has raised a global uproar as regards its use in humans, especially after the 2018 announcement of a Chinese scientist who had used CRISPR to edit the genes of twin embryos. Indeed, one of the greatest concerns, although not the only one, has been the use of genome editing technologies to modify the human germline. In such scientific and technological context, the law plays a key role in framing what should be allowed or prohibited, and under which conditions, to find a balance between safe and accessible innovative treatments and respect of fundamental rights in accordance with the societal values and choices. Within the European Union, several institutions have considered the issues raised by human genome editing, and several legal texts participate in the establishment of the European regulatory framework applicable to human genome editing. Yet we argue in this article that the established regulatory landscape is fragmented in the sense of being divided, split, or segmented. Such fragmentation, which may have been inevitable for historical and technicolegal reasons, produces effects regarding the role of the current regulatory frameworks applicable to human genome editing. Focusing on the European Union and on the French levels of governance, we discuss how such fragmentation takes place through the identification of determinants of the human genome editing fragmented regulatory landscape. We argue that it should be seen as a process providing more contingent responses to human genome editing reflecting changing political and legal contexts.

Keywords: human genome editing, European Union law, French law, fragmentation, regulatory landscape

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INTRODUCTION

Genome editing techniques have generated a growing interest following the discovery of the so-called CRISPR-Cas ("Clustered Regularly Interspaced Palindromic Repeats–Cas") technique (Hsu et al., 2014). It has raised a global uproar as regards its use in humans, especially after the 2018 announcement of a Chinese scientist who had used CRISPR to edit the genes of twin embryos (Greely, 2019). Indeed, one of the greatest concerns, although not the only one, has been the use of genome editing technologies to modify the human germline (Almqvist and Romano, 2020). In such scientific and technological context, the law plays a key role in framing what should be allowed or prohibited, and under which conditions, to find a balance between

safe and accessible innovative treatments and respect of fundamental rights in accordance with the societal values and choices. Whereas several initiatives have aimed at providing ethical and policy-oriented guidance,[1] it is the role of the law to adopt the binding rules to support such innovation and to determine the technological limits of what is acceptable for a society. Nevertheless, formal law is not a stand-alone norm to orient societal conducts, and it is tightly related to evolving political contexts. Indeed, we will show below that several organizations have considered the issues raised by human genome editing and several "norms," here understood as encompassing both formal law and regulations, and texts from nonlegal organizations aiming at regulating societal conducts, participate in the establishment of the European normative framework applicable to human genome editing within the European Union (EU). The EU level of governance is particularly interesting to explore as it has emerged as a legal and policy domain in the field of health law and policy (Guy and Sauer, 2017). It is also the most advanced legal system aiming at interstate collaborations, ranging from mere cooperation to harmonization, with binding jurisdictional mechanisms for implementation and interpretation of the law (Rieder, 2017).[2] As we will see below, EU law is far to be exempted from legal considerations on human genome editing, although this level of governance has often been overlooked in the literature. Indeed, much attention in legal scholarship was first given to national levels, often in a comparative approach (Araki and Ishii, 2014), or to the international level (Rosemann et al., 2019), including linking human rights law and biotechnologies (Francioni, 2007; Murphy, 2009). Nevertheless, a developing literature already explains how EU law applies throughout the development pipeline for new technologies more generally (Flear, 2017). More specific articles now discuss the current regulatory European framework (EU and Council of Europe levels)[3] on human germline modification (Almqvist and Romano, 2020; Nordberg et al., 2020), the focus of EU legislations on technical risks (Mahalatchimy and Rial-Sebbag, 2020), or the imaginary built into its framing (Mahalatchimy et al., 2021).

Building on this literature, we argue in this article that the established regulatory landscape is fragmented in the sense of being divided, split, or segmented. The phenomenon of fragmentation of the law (dispersal) is particularly discussed in international law. Usually, discussions start from the assumption that fragmentation must be occurring and then primarily tackle the problems it creates (Martineau, 2015). In contrast, we can consider fragmentation as a process that provides more contingent responses to human genome editing reflecting changing political and legal contexts. We will focus on how fragmentation is occurring at the EU level,[4] and we will take French law as a case study (Blasimme et al., 2020; Rial-Sebbag, 2020)[5] of implementation of EU law, including the last developments adopted from the French Bioethics Law (lastly revised in August 2021).[6] We will discuss three aspects of this regulatory landscape's fragmentation. The first aspect is the territorial fragmentation occurring within the European regulatory landscape on human gene editing. Indeed, this landscape is constituted by both EU law and national Member State laws. Through the case study of French law, we will highlight which considerations of human genome editing are regulated by EU and French laws and why. The second aspect is the substantive fragmentation that occurs within the law applicable to human genome editing. Indeed, several legal instruments constitute this regulatory framework. They relate to the regulated objects (tissues and cells, genetically modified organisms [GMOs], advanced therapy medicinal products), the stages of development of medicines based on human genome editing (fundamental research, patentability, clinical trials, marketing authorization), or the regulated field (civil law, public health law, Bioethics Law). The third aspect is the institutional fragmentation of the European regulatory landscape on human gene editing. Here we will show that activities on human genome editing are governed not only by French state and EU institutions, but also by European organizations that represent specific communities. It involves a set of rules with various authoritative weights. In the last part, we identify determinants of the human genome editing fragmented regulatory landscape that contribute to fragmentation as a process to adapt to the changing political and legal contexts.

TERRITORIAL FRAGMENTATION

The European regulatory landscape on human genome editing is fragmented at the territorial level. Such fragmentation comes from the legal status of the EU itself that has evolved from the

[1]See as an example the "Human Genome Initiative" set up under the umbrella of The National Academies of Sciences, Engineering, and Medicine, https://www.nationalacademies.org/our-work/human-gene-editing-initiative (last accessed November 17, 2021).

[2]Both actual litigation and the "shadow of litigation," which may be important, have to be taken into account.

[3]Even though out of the scope of this article, we recall that the Oviedo Convention bans interventions aiming at human germline modification and limits the purposes of any intervention on the human genome, including in the field of research, to prevention, diagnosis, or therapy according to its article 13: "An intervention seeking to modify the human genome may only be undertaken for preventive, diagnostic, or therapeutic purposes and only if its aim is not to introduce any modification in the genome of any descendants." The Committee on Bioethics of the Council of Europe has established a drafting group in order to "provide clarifications on the terms "preventive, diagnostic, and therapeutic" and to avoid misinterpretation of the applicability of this provision to "research." Council of Europe, Committee on Bioethics, 18th meeting, June 1–4, 2021, DH-BIO/Abr RAP18. France has signed (1997) and ratified (2011) this convention producing direct effects in its national legal framework.

[4]We are not covering in this article the links between EU law and international law (for instance the Oviedo Convention) because of the limited space and the specificity of the legal principles and mechanisms involved.

[5]For articles fully dedicated to the French frameworks.

[6]Law n°2021-2017 of 2 August 2021 on Bioethics, OJ n°0178 of 3 August 2021, text n°1.

funding treaties to the current applicable and so-called "Lisbon Treaty" including both the Treaty on the Functioning of the European Union (TFEU) and the Treaty on the European Union. First, the EU is organized in accordance with a legal sharing of competences between the EU as an organization and its Member States. Such sharing relies generally on four types of competence: exclusive EU competences, complementary EU competences, shared competences between the EU and its Member States, and exclusive Member States competences (Konstadinides, 2018). The areas the most relevant to human genome editing belong to the shared competences between the EU and its Member States or to the complementary EU competence regarding internal market, research, and public health. Consequently, EU and national laws have to adapt and to interact according to their competencies. The protection and improvement of human health are an area of primary national competence where the EU can only act according to its complementary competence,[7] meaning that the EU can only intervene to "support, coordinate, or supplement the actions of the Member States, without thereby superseding their competence in these areas" and that legally binding EU acts "shall not entail harmonization of Member States' laws or regulations."[8] However, the EU competence in public health has been strengthened (Hervey and McHale, 2015; Guy and Sauer, 2017), and it also includes now the shared competence in some common safety concerns in public health matters[9] where both the EU and its Member States are able to legislate and adopt legally binding acts: Member States exercise their own competence to the extent that the EU has not exercised or has decided to cease exercising its own competence.[10] According to the latter, the EU can adopt regulations in order to ensure "a high level of human health protection,"[11] which has often been combined with the achievement of the internal market,[12] the "protection of human health" having to be taken into account in all EU policies and activities.[13] The EU competency in research has also evolved as a specific shared competence (De Grove-Valdeyron, 2018) as long as its exercise "shall not result in Member States being prevented from exercising [their competences]."[14] This mechanistic approach on "who does what" could lead to a reduced vision on how the EU has used these legal bases to intervene in the field of health. In particular, article 114 TFUE has served as a (too) broad basis for the EU to legislate on numerous and various technologies with a focus on their commercial potential and their risks according to economic and political interests especially during the 1980s and 1990s (Hervey and McHale, 2015, 34–40). This has led to an extended framework for emerging technologies in health at the EU level, which has nevertheless been restrained by the limited EU competencies for other objectives than the internal market, especially as regards public health and research. Therefore, national laws remain primary regarding some aspects of new health technologies, including human genome editing techniques, in particular regarding the moral imperatives related to innovations, whereas EU law is clearly dominant to regulate these techniques for commercial objectives. Thus, these legal mechanisms reflect the role of the regulation in balancing the support to the development of technical advances in health and the management of their potential risks (technical and societal) for European citizens at European and national levels in accordance with various objectives. Although the resulting legal environment appears complex and sometimes unclear or even hazardous for technology developers as well as for citizens, it also highlights how fragmentation of applicable laws allows to take into account the political context of the EU governance of technology and its dynamics, such as the evolution of the sharing of competences between the EU and its Member States.

Consequently, the European regulatory landscape on human genome editing is territorially fragmented as it is constituted both by EU law that is implemented similarly in all EU Member States and by various national Member States laws. Through the case study of French law, we will highlight which considerations of human genome editing are regulated by EU and French laws and why. Here the laws distinguish human genome editing for research and for therapy (Mahalatchimy and Rial-Sebbag, 2020).[15]

Regarding human genome editing for research, fundamental and clinical research relies on different legal frameworks. While fundamental research is mainly regulated by national laws and accessorily by EU law, it is the contrary for clinical research. As long as genome editing technologies involve that human biological samples are to be used, the legal framework regarding fundamental research relies, first, on French law[16] for the collection of the samples and, second, on EU law for the safety rules.[17] This combination implies that researchers have to comply with the respect of individual fundamental rights as stated in the French legal framework and that the laboratories fulfill common EU safety requirements.

Regarding human genome editing for therapy, EU law is dominant regarding medicinal products based on human genome editing techniques, manufactured at the industrial scale and intended to be placed on the EU market. Indeed, the specific and unified legal regime established by Regulation (EC) n°1,394/2007 on Advanced Therapy Medicinal Products (ATMPs) applies.[18] However, where the medicinal products

[7]Article 6 TFEU.
[8]Article 2§5 TFEU.
[9]Article 4 TFEU.
[10]Article 2§2 TFEU.
[11]Article 168, TFEU.
[12]Article 114, TFEU.
[13]Article 168§1 TFEU.
[14]Article 4§3 TFEU.

[15]For an article providing a detailed analysis of how EU law regulates human genome editing for research and therapy.
[16]Law on research involving human person (2012) and Bioethics Law for research on embryos (2021).
[17]Mainly Directive 2004/23/EC of the European Parliament and of the Council of March 31, 2004, on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage, and distribution of human tissues and cells, OJ L 102, 7.4.2004, pp. 48–58, and its implementation directives of 2006 and 2015.
[18]Regulation (EC) n°1,394/2007 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) n°726/2004, OJ L324, 10.12.2007, p.121.

based on human genome editing techniques are "prepared on a nonroutine basis according to specific quality standards, and used within the same Member State in a hospital under the exclusive responsibility of a medical practitioner, in order to comply with an individual medical prescription for a custom-made product for an individual patient," they are regulated under national laws.[19] Moreover, where the products based on human genome editing techniques for therapy do not fall within the exact definitions of ATMPs, they are regulated at national levels if they are not manufactured at the industrial scale and not intended to be placed on the EU market. This dichotomy based on the clearly stated legal sharing of competencies between EU and its Member States has led to some blurring on how to identify the correct level of rules to be applied to genome editing techniques, creating some legal insecurity to the various stakeholders (Mourby and Morrison, 2020).

Thus, human gene editing technologies are regulated both by EU law and national laws, and as such, the regulatory landscape is territorially fragmented.

SUBSTANTIVE FRAGMENTATION

The second aspect is the substantive fragmentation that occurs within the law applicable to human genome editing. On the one hand, substantive fragmentation is the direct consequence of territorial fragmentation as it has been explained above regarding fundamental and clinical research, for instance. On the other hand, the legal landscape of human genome editing is also fragmented substantively at the EU level as long as there is currently no common and explicit EU legal approach on genomics[20] and on human genome editing. Nevertheless, several European legislations provide legal frameworks applicable to human genome editing.

First, the EU's Legal Protection of Biotechnological Inventions Directive[21] (Biotechnology Directive) allows to obtain a patent for inventions based on biological elements where three main criteria are met: the invention is new, it involves an inventive step, and it is susceptible of industrial application.[22] In this context, the isolation or production by means of a technical process of a product consisting of or containing biological material, such as the sequence or partial sequence of a gene, may be a patentable invention, even if the structure of that element is identical to that of a natural element.[23] Nevertheless, "the human body, at the various stages of its formation and development, and the simple discovery of one of its elements, including the sequence or partial sequence of a gene, cannot constitute patentable inventions."[24] Consequently, inventions based on human genome editing techniques are patentable under EU law. However, two main exclusions limit the extent of their patentability.

The Biotechnology Directive provides for moral and ethics exclusions to the patentability of biotechnological inventions where their commercial exploitation would be contrary to "order public or morality."[25] Within the nonexhaustive and indicative list of processes to which the exclusion from patentability applies, all items are relevant to genome editing. The first two ones are directly related to human genome editing as they mention "processes for cloning human beings"[26] and "processes for modifying the germline genetic identity of human beings" (Li, 2014; Wong and Mahalatchimy, 2018; Mahalatchimy et al., 2021).[27] The last two ones are indirectly related to human genome editing. Indeed, the exclusion of the "uses of human embryos for industrial or commercial purposes"[28] introduces additional limits to genome editing on human embryos that go beyond the modification of the human germline genetic identity. As such, it limits the patentability of inventions based on genome editing in human embryos at a later stage of their development as long as the "prior destruction of human embryos or their use as base material, whatever the stage at which that takes place" excludes an invention from patentability.[29] Finally, the exclusion of "processes for modifying the genetic identity of animals, which are likely to cause them suffering without any substantial medical benefit to man or animal, and also animals resulting from such processes" limits the patentability of these inventions at the preclinical stage of gene editing technologies' development. The Biotechnology Directive also provides for a medical treatment exclusion as long as it excludes from patentability "methods of therapeutic, diagnostic and surgical treatment on the human or animal body."[30]

Beyond these main rules, the patent regulatory landscape is complex as highlighted by the battles of priority and claims regarding patents linked to CRISPR-Cas9, and opposing mainly the University of California (UC) together with the University of Vienna (referred to as CVC), and the Broad Institute in Cambridge (the Broad), Massachusetts, both in the United States and in Europe. While UC claims patent rights for the uses of CRISPR in all types of cells, the Broad claims them for their uses in eukaryotes, a key area to develop human medicines. Although the battle is still ongoing (Cohen, 2020), the United States Patent and Trademark Office seems to have ruled more in favor of the Broad, but it seems to be the opposite for the European Patent office (Cohen, 2017a). Nevertheless, the issues at stake on overlapping or shared patent rights are wider (Feeney et al., 2018), notably as they involve other parties that have filed early CRISPR claims with patent offices (Cohen, 2017b).

[19]Recital (6) and article 28.2 of Regulation (CE) n°1,394/2007.

[20]JRC Science for Policy Report, Overview of EU national legislation on genomics, 2018, p. 74.

[21]Directive 98/44/EC on the Legal Protection of Biotechnological Inventions, OJ 1998 L 213/13.

[22]Article 4 Directive 98/44/EC, *ibid*.

[23]Article 5 (2) Directive 98/44/EC, *ibid*.

[24]Article 5 (1) Directive 98/44/EC, *ibid*.

[25]Article 6 Directive 98/44/EC, *ibid*.

[26]Article 6(2) (a) Directive 98/44/EC, *ibid*.

[27]Article 6(2) (b) Directive 98/44/EC, *ibid*.

[28]Article 6(2) (c) Directive 98/44/EC, *ibid*.

[29]CJEU, Grand Chamber, Brüstle v Greenpeace eV (C-34/10) [2011] E.C.R. I-9821 [2012] 1 C.M.L.R. 41, at 52.

[30]Recital 35 Directive 98/44/EC, *ibid*.

Second, two main EU legal instruments apply to research on human genome editing techniques. Research on human genome editing techniques can be funded by the EU as long as it complies with the current Framework Programme for Research and Innovation for 2021–2027, "Horizon Europe."[31] On the one hand, it shall comply with "ethical principles and relevant national, Union, and international legislation, including the Charter of Fundamental Rights of the EU and the European Convention on Human Rights and its Supplementary Protocols."[32] On the other hand, it excludes from funding "activities intended to modify the genetic heritage of human beings, which could make such modifications heritable"[33] as well as the funding of research that is prohibited in all Member States or in a Member State where such research activity is forbidden.[34] On such legal basis, "EU has funded research projects across genome editing technologies, in particular in the biomedical sector" but also in agriculture, ecosystems, and insects.[35]

Moreover, the clinical trials regulation[36] applies to medicines based on human genome editing techniques, especially regarding advanced therapy medicinal products,[37] and provides the same requirements as for any other medicinal products in order to generate "reliable and robust data."[38] Safety in clinical trials stems from the investigational medicinal product and the intervention[39] that are assessed by national competent authorities and ethics committees in order to authorize the start of the clinical trials. The only specificity mentioned by this regulation regarding clinical trials of advanced therapy medicinal products concerns the period for producing this evaluation and the possibility for the reporting Member State[40] to extend it by a further 50 days for the purpose of consulting experts.[41] However, specific Good Clinical Practice applies to advanced therapy medicinal products.[42] Neither these guidelines nor the report of the EMA expert meeting on genome editing technologies used in medicinal products provides for specificities regarding clinical aspects due to insufficient clinical evidences.[43]

Most importantly, the clinical trials regulation prohibits to carry out "gene therapy clinical trials, which result in modifications to the subject's germline genetic identity."[44] "As of March 2021, no clinical trials of *in vivo* genome editing are known to be underway in the EU but a few trials using *ex vivo* genome editing, to modify autologous cells, are reported in the EU Clinical Trials Register."[45]

Apart from the aforementioned European legal instruments providing rules for clinical research and research funding and by opposition to French law (see below), the EU has not adopted specific rules regarding the uses of biological samples in fundamental research[46] and *a fortiori* in the context of human genome editing. Nevertheless, the safety of human tissues and cells is framed by EU law by the Tissues and Cells Directives,[47] as long as they are used for human applications, such as graft or more widely therapy. Legally, these directives do not apply in research. Nevertheless, they guide the overall safety and health risk management expectations of establishments using human cells. As in practice, biobanks generally combined health safety and research objectives; they apply the higher safety standards provided by the European Directives on Tissues and Cells for their activities, be the tissues and cells used for therapy or for research.

Third, although there is no authorized medicinal product that use genome editing as of mid-2020,[48] therapies using genome editing techniques will be regulated by the European regulation on ATMPs,[49] as long as they fall under its scope as explained above in 2). This regulation is stricter in terms of risk assessment than that provided for other medicinal products, because of the innovative nature and the complexity of the manufacturing processes of ATMPs. It also provides regulatory incentives for their development and their market access, such as European Medicines Agency's fees reduction. In order for the European Commission to grant the authorization decision, ATMPs have to go through the centralized European Marketing Authorization procedure. This involves the opinion of the Committee for

[31]Regulation (EU) 2021/695 of the European Parliament and of the Council of 28 April 2021 establishing Horizon Europe—the Framework Programme for Research and Innovation, laying down its rules for participation and dissemination, and repealing Regulations (EU) No 1290/2013 and (EU) No 1291/2013, OJ L170 of 12.5.2021, pp. 1–68.

[32]Article 19§1 of Regulation (EU) 2021/695, *ibid*.

[33]Article 18§1 b) of Regulation (EU) 2021/695, *op. cit*. This article also excludes at §1: "a) activities aiming at human cloning for reproductive purposes" and "c) activities intended to create human embryos solely for the purpose of research or for the purpose of stem cell procurement, including by means of somatic cell nuclear transfer."

[34]Article 18§2 of Regulation (EU) 2021/695, *op. cit*.

[35]"There are about 200 EU projects in the CORDIS database containing "gene editing" in their description." European Medicines Agency and Heads of Medicines Agencies. Genome editing EU-IN Horizon Scanning Report, February 15, 2021, EMA/319248/2020, p. 10.

[36]Regulation (EU) 536/2014 on Clinical Trials on Medicinal Products for Human Use, and Repealing Directive 2001/20/EC, OJ 2014 L 158/1.

[37]An investigational medicinal product that is an advanced therapy medicinal product as defined by Regulation (EC) n°1,394/2007.

[38]Article 3b) of Regulation (EU) 536/2014, *op. cit*.

[39]Recital (11) of Regulation (EU) 536/2014, *op. cit*.

[40]The Member State designated to conduct the clinical assessment.

[41]Article 6§7 of Regulation (EU) 536/2014, *op. cit*.

[42]European Commission, Guidelines on Good Clinical Practice specific to advanced therapy medicinal products, October 10, 2019, C(2019) 7,140 final.

[43]EMA, *Report of the EMA Expert Meeting on Genome Editing Technologies Used in Medicinal Product Development* (2018), EMA/47066/2018.

[44]Article 90 of Regulation (EU) 536/2014, *op. cit*., which maintains this prohibition as established by previous Directive 2001/20/EC 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, OJ 2001 L 121/34.

[45]European Medicines Agency and Heads of Medicines Agencies. Genome Editing EU-IN Horizon Scanning Report, *op. cit*. p. 4.

[46]Biobanks for Europe: a challenge for governance, Directorate-General for Research and Innovation (European Commission), https://op.europa.eu/en/publication-detail/-/publication/629eae10-53fc-4a52-adc2-210d4fcad8f2 (last accessed November 17, 2021).

[47]Directive 2004/23/EC and its implementation directives of 2006 and 2015, *op. cit*.

[48]European Medicines Agency and Heads of Medicines Agencies. Genome Editing EU-IN Horizon Scanning Report, *op. cit*. p. 4.

[49]Regulation (EC) 1,394/2007 on Advanced Therapy Medicinal Products and Amending Directive 2001/83/EC and Regulation (EC) 726/2004, OJ 2007 L 324/121.

Advanced Therapies, in addition to that of the Committee for Medicinal Products for Human Use, within the European Medicines Agency (EMA). Generally, safety requirements are strengthened, and specific guidelines related to good clinical, manufacturing, and pharmacovigilance practices apply. However, although it is very likely that therapies using genome editing techniques will be considered as ATMPs, it will be more challenging to determine in which type of ATMPs they will be classified into. Indeed, Mourby and Morrison have suggested that nucleic acids not produced by recombination, and protein-based molecules, which are also gene-editing techniques, may fall outside the scope of the definition of gene therapy medicinal products within the ATMP Regulation, which focuses on gene therapies containing or consisting of recombinant nucleic acid (Mourby and Morrison, 2020). Moreover, on the basis of existing scientific guidelines[50] we have previously explained that if cells that have been genetically modified by genome editing techniques are developed to use a targeted genetic sequence for therapeutic purposes, it should be a gene therapy medicinal product. However, if these cells are used for manufacturing purposes in the development of cell or tissue therapy, it should be a cell therapy medicinal product or a tissue-engineered product (Mahalatchimy and Rial-Sebbag, 2020).

Fourth, the legislations on GMOs[51] and genetically modified micro-organisms (GMMOs) apply.[52] Directive 2009/41/EC on the contained use of GMMOs applies to human genome editing techniques taking place in laboratories as long as these techniques fall into the scope of this directive. The latter is limited by the legal definition of GMMOs: "any microbiological entity, cellular or noncellular, capable of replication or of transferring genetic material, including viruses, viroids, and animal and plant cells in culture."[53] It is thus related to techniques using vectors. However, it is unclear whether the use of other genomic techniques in human genome editing is covered by this directive. Directive 2009/41/EC establishes risk assessment procedures according to four classes of GMMOs in order to obtain receipt or authorization of their contained use from the national competent authority. Directive 2001/18/EC on the deliberate release into the environment of GMOs provides a risk assessment methodology over time, based on principles to identify the negative impacts that the GMO release could produce.[54] The assessment aims to determine the GMO classification according to their level of risk concerning the security of the premises. Directive 2001/18/EC applies to edited human cells when the genetic manipulations carried out are those described by the directive in the legal definition of GMOs: "an organism, with the exception of human beings, in which the genetic material has been altered in a way that does not occur naturally by mating and/or natural recombination."[55] But the extent of the application of the said directive to human genome editing techniques and the modalities of its implementation remain unclear in two respects in particular. On the one hand, "human beings" are excluded from the legal definition of GMOs, as long as "genetically modified human beings" were unthinkable at the time of adoption of Directive 2001/18/EC. On the other hand, in Confédération paysanne and Others v. Premier ministre and Ministre de l'Agriculture, de l'Agroalimentaire et de la Forêt, the Court of Justice of the European Union rules out that organisms obtained by mutagenesis are to be classified as GMOs, as the genetic material of an organism is altered by the techniques and methods of mutagenesis in a way that does not occur naturally.[56] Therefore, the Court has clarified that genome editing techniques are covered by the directive in an extensive manner as not only the manipulations of transgenesis (insertion of a gene) are concerned but also those of mutagenesis. However, the latter case law applies only to the field of plants, and it remains uncertain this interpretation would cover the technique of mutagenesis applied to human genetic material. Clarification on such aspect did not occur within the European Commission's study, requested by the Council of the European Union,[57] on the status of new genomic techniques under EU law.[58] Nevertheless, the European Commission highlighted that the application of the GMO legislation to medicines, as it is for medicines based on human genome editing techniques, "hinders the development of these products in the EU."[59] Indeed, during a public consultation preceding this study, Member States and other stakeholders underlined challenges of applying the current GMO legislation to medicinal products for human use such as duplication of assessment by medicines and environmental agencies,[60] complex and lengthy process for gaining approval of clinical trials with products consisting of or containing GMOs,[61] and public information and understanding.[62] These issues have been referred back to the EU pharmaceutical strategy.[63] Hence, the European Commission will

[50]Mainly EMA, Guideline on quality, non-clinical and clinical aspects of gene therapy medicinal products, 22 March 2018, EMA/CAT/80183/2014; and EMA, Guideline on Quality, Non-clinical and Clinical Aspects of Medicinal Products Containing Genetically Modified Cells, November 12, 2020, EMA/CAT/GTWP/671639/2008 Rev. 1—corr.

[51]Directive 2001/18/EC on the Deliberate Release Into the Environment of Genetically Modified Organisms and Repealing Directive 90/220/EEC, OJ 2001 L 106/1.

[52]Directive 2009/41/EC on the Contained Use of Genetically Modified Micro-organisms, OJ 2009 L 125/75.

[53]Article 2§a of Directive 2009/41/EC, *ibid.*

[54]Annex II of DIRECTIVE 2001/18/EC, *op. cit.*

[55]Article 2§1 of DIRECTIVE 2001/18/EC, *op. cit.*

[56]Case C-528/16 Confédération paysanne and Others v. Premier ministre and Ministre de l'Agriculture, de l'Agroalimentaire et de la Forêt [2018] (ECLI:EU:C:2018:583).

[57]Council Decision (EU) 2019/1904 of November 8, 2019, requesting the commission to submit a study in light of the Court of Justice's judgment in Case C-528/16 regarding the status of novel genomic techniques under Union law, and a proposal, if appropriate in view of the outcomes of the study, JO L 293 du 14.11.2019, pp. 103–104.

[58]European Commission, Commission staff working document, study on the status of new genomic techniques under Union law and in light of the Court of Justice ruling in Case C-528/16, April 29, 2021, SWD (2021) 92 final.

[59]*Ibid.* p. 59.

[60]Europabio's answer to the Stakeholder Questionnaire on new genomic techniques to contribute to a commission study requested by the Council, May 15, 2020.

[61]Alliance for Regenerative Medicine's answer to the Stakeholder Questionnaire on new genomic techniques to contribute to a commission study requested by the Council, May 15, 2020.

[62]France's answer to the Stakeholder Questionnaire on new genomic techniques to contribute to a commission study requested by the Council, July 3, 2020.

[63]European Commission, Commission staff working document, study on the status of new genomic techniques under Union law and in light of the Court of Justice ruling in Case C-528/16, *op. cit.* p. 59.

explore solutions during the evaluation of the pharmaceutical legislation in 2022 in order to "consider adapting regulatory requirements in the pharmaceutical legislation, applicable to medicines for human use that contain or consist of genetically modified organisms."[64]

As a result, even if some rules are stated at the EU level, some of them remain unclear especially because of the little experience in the field and because of the fact that most of the legal requirements on the use of genome editing techniques are provided by national legislations.

At the French national level, the rules that apply to human genome editing are not embedded within one clear regulatory framework, and two pieces of legislation are concerned. The Bioethics Laws as adopted in 1994[65] aimed at enacting fundamental rights to protect the human body and its parts[66] and at applying these principles in medical and research practices.[67]

First, the core principles regarding the protection of the human genome are enacted in the Civil Code (CC). This code aims at regulating the status of individuals and their relationships. Since the adoption of the first Bioethics Laws as partly implemented in this code,[68] the CC also recognizes a status for the human species and their integrity.[69] Thus, genome editing techniques leading to any modification of the human genome that should be transmitted to the next generation is considered unlawful.[70] Second, the applications in health care are covered by the provisions of the Public Health Code (PHC), which is regulating the implementation of genetic technologies in alive humans and in embryos. The previous version of the Bioethics Laws (of 2011) had not identified genome editing as a key question because it was not so much developed at that time. Several provisions of the PHC[71] were in alignment with the ban of genome editing as stated in the CC where genome editing was supposed to be conducted as an intervention on embryos leading to birth. However, the provisions related to research activities in this field were unclear and the French legal framework was unable to secure the activities of French researchers. As a consequence, heated debates and controversies occurred during the revision process of the Bioethics Law recently published in August 2021 in order to clarify whether the ban of using genome editing techniques was only applying to therapeutic/diagnosis interventions in embryos or also to research activities.

To date, the legal provisions are clearer and should distinguish two main cases. The first refers to the use in research of genome editing techniques in alive humans to treat somatic cells. As long as this intervention is used only in somatic cells to treat a disease and cannot be transmitted to the offspring, it is qualified as a gene therapy. In this context, the research is lawful as long as the fundamental principles and procedures ensure the respect of voluntary participation and follow the rules attached to the collection, storage, and use of human biological materials as stated in the PHC. Clinical trials are also permitted under the umbrella of the European law (Clinical Trial Regulation and ATMP Regulation, see above). However, the genome editing regulatory landscape is even more fragmented when it comes to its use in embryos. The use of genome editing techniques in embryos and human embryonic stem cells (hESCs) is more problematic given the germline modifications involved. Despite quick references to hESCs in European law, the framing of their use occurs mainly in national regulations (Isasi et al., 2016). The adoption of the new 2021 Bioethics Law, after strong debates in the two parliamentary assemblies, clarified the legal landscape. As a result, according to the new article L2151-2 PHC, the ban to use heritable genome editing as a therapeutic intervention is maintained, but the research is now specifically allowed. This clear support to research activities results from the removal of the ban to create transgenic embryos as previously stated in the law.

The research protocol evaluation will be in the hands of the competent authority (Agence Nationale de Sécurité du Médicament et des produits de santé) and of the Research Ethics Committee (in France Comité de Protection des personnes) for research on somatic cells. The Biomedicine Agency (Agence de la Biomédecine) is the national competent authority for research on embryos and hESCs. They will be particularly in charge of compliance with safety requirements as stated in the European Regulations and fundamental rights as stated in the Bioethics Law.

Thus, the substantive fragmentation occurs both in EU and French laws as regards fundamental research and clinical research, research and therapy, or genome editing on somatic cells and on embryos and hESCs.

The fragmentation as observed regarding the territorial and substantive landscapes is also perceptible when it comes to institutions.

INSTITUTIONAL FRAGMENTATION

The third aspect is the institutional fragmentation of the European regulatory landscape on human gene editing.

[64]Communication from the Commission to the European Parliament, the Council, the European Economic and Social Committee and the Committee of the Regions, Pharmaceutical Strategy for Europe, November 25, 2020, COM (2020)761 final, p. 16.

[65]These laws were initially adopted in 1994 with a principle of periodic revisions that occurred in 2004, 2011, and 2021.

[66]Loi n°94-653 du 29 juillet 1994 relative au respect du corps humain (respect for the human body).

[67]Loi n°94-954 du 29 Juillet 1994 relative au don et à l'utilisation des éléments et produits du corps humain, à l'assistance médicale à la procréation et au diagnostic prénatal (donation and use of human body parts and products, medically assisted procreation, and prenatal diagnosis).

[68]The law n°94-653 has been implemented in the CC.

[69]Civil Code art. 16-4: No one may infringe upon the integrity of mankind. Any eugenic practice that aims at organizing the selection of persons is forbidden. Any medical procedure whose purpose is to cause the birth of a child genetically identical to another person alive or dead is forbidden. Without prejudice to research aimed at the prevention, diagnosis, and treatment of diseases, no transformation may be made to genetic characteristics with the aim of modifying the person's descendants.

[70]*Ibid.*

[71]Article L2151-2 PHC was banning the creation of transgenic and chimeric embryos, and article L2151-5 IV was banning the reimplantation of embryos after research for the purpose of giving birth.

Beyond the regulatory frameworks, strictly considered as "state law,"[72] which apply to human genome editing, several European organizations have highlighted the societal challenges and their related ethical principles regarding human genome editing.

Regarding the EU institutions, and beyond the aforementioned EMA's technical report, both the European Commission[73] and the European Parliament[74] have provided a state of the challenges raised by human genome editing. The European Group on Ethics in Science and New Technologies is the one that has gone deeper on these aspects with a 2016 statement[75] and a more complete 2021 opinion on the ethics of genome editing.[76] The Council of the EU has considered genome editing regarding GMOs in plants only in its request to the European Commission to conduct the study on the status of novel genomic techniques under Union law, with the latter sending back the issues to the EU pharmaceutical strategy as mentioned previously.

In parallel to the classical EU bodies, several European organizations that represent specific communities have gone beyond highlighting the societal challenges raised by human genome editing in providing recommendations. These organizations are the Federation of European Academies of Medicine,[77] the European Academies Science Advisory Council,[78] the European Society of Human Reproduction and Embryology, and the European Society of Human Genetics together (de Wert et al., 2018), and the Patients Network for Medical Research and Health.[79]

At the national level, here concerning France, both governmental institutions and other organizations have tackled human genome editing.[80] In addition to the clarifications adopted by the new French Bioethics Law[81] on which activities can be considered as lawful and which are still forbidden, medical institutions, namely, academia, as well as several ethics committees, have taken position (see below).

The parliamentary debates occurring during the revision process of the Bioethics Law[82] (2019–2021) show a strong opposition between the Senate and the National Assembly. The proposal of opening genome editing of embryos and hESCs to research activities was strongly supported by the National Assembly in the name of advancing science and of making innovations available to researchers. The arguments were developed on the ground of technology advancement, of benefit for knowledge, and, most of all, of keeping French research activities' competitiveness. On the contrary, the Senate based its reluctance on moral arguments, stating that opening these activities would favor human selection and would open rooms for eugenics. The last version of the law, as adopted by the National Assembly, was submitted to the Constitutional Council[83] after a referral from the Senate. In this decision, the Council states that according to all the requirements already enacted in the Bioethics Law regarding the authorization of the research protocols on embryos and hESCs, all the necessary safeguards[84] are in place to lawfully conduct this research and that this change of the law is not contrary to the respect of the human dignity principle.

Regarding academia, two main institutions (Academia of Medicine and Academia of Sciences) have elaborated statements, before the adoption of the Bioethics Law, then contributing to the debate. We can underline here that they were representing the voice of medical and scientific practitioners. The Academia of Sciences,[85] rather than providing a report or full statement regarding genome editing, organized several scientific manifestations or public events. Then, in its recommendations in the scope of the revision of the Bioethics Law,[86] they focused on the ethical and societal questions raised by genome editing in plants and in animals. However, after the twins' birth in China, the Academia of Sciences joined the Academia of Medicine to ban Dr He Jianku's initiative through the adoption of a joint declaration.[87] Both academia insisted on the lack of knowledge regarding genome editing uses in practice and added that "in the current state of knowledge, the conditions are not met to open the way to the birth of children whose genome has been modified in the embryonic state." Moreover, the Academia of Medicine issued a report in 2016 where academicians stated that "while avoiding the transmission of a genetic disorder to a child could be an acceptable indication for modification of the unborn child's genome, the conditions are currently far from being met for

[72]Although the European Union is a European organization and not a state, we use "state law" in the meaning of law established through a population-level democracy process.

[73]European Commission and European Group on Ethics, Open Round Table on the Ethics of Gene Editing, October 16, 2019: https://ec.europa.eu/info/events/round-table-ethics-gene-editing-2019-oct-16_en.

[74]European Parliament, What if gene editing became routine practice? October 16, 2018. https://www.europarl.europa.eu/RegData/etudes/ATAG/2018/624260/EPRS_ATA(2018)624,260_EN.pdf.

[75]European Group on Ethics in Science and New Technologies, statement on gene editing, 2016.

[76]European Group on Ethics in Science and New Technologies, Opinion n°32 on the ethics of genome editing, March 19, 2021.

[77]Federation of European Academies of Medicine. Human genome editing in EU, Report of a workshop held on April 28, 2016, at the French Academy of Medicine, 2016.

[78]European Academies Science Advisory Council (EASAC). Genome editing: scientific opportunities, public interests and policy options in the European Union. EASAC policy report 31, 2017.

[79]Patients Network for Medical Research and Health. Gene editing and the patient's perspective, 28 September 2017: https://egan.eu/news/gene-editing-and-the-patients-perspective/.

[80]We will highlight those that can be considered as the most representative.

[81]*Supra*.

[82]For a full picture of the process, see Senate's documentation, https://www.senat.fr/dossier-legislatif/pjl19-063.html.

[83]Decision of the Constitutional Council n° 2021-821 DC of July 29, 2021, available at https://www.conseil-constitutionnel.fr/decision/2021/2021821DC.htm.

[84]Such as a written protocol submitted to an independent Agency (Agence de la Biomédecine), the assessment of the scientific and ethics validity and the justification to use embryos or hESCs.

[85]https://www.academie-sciences.fr/fr/.

[86]https://www.academie-sciences.fr/fr/Rapports-ouvrages-avis-et-recommandations-de-l-Academie/revision-de-la-loi-de-bioethique.html.

[87]https://www.academie-sciences.fr/fr/Rapports-ouvrages-avis-et-recommandations-de-l-Academie/bebe-genetiquement-modifie.html.

such an approach to be clinically feasible."[88] Thus, rather than banning genome editing in embryos for moral reasons, the Academia built its argumentation on the lack of knowledge regarding the risks of implementing this new technology and identified several other options that would be available and lawful for couples to help them in their parental project (such as adoption, gametes donation. . .).

Finally, several ethics committees[89] expressed their concerns regarding the deployment of genome editing. We will insist on the opinion issued by the National Ethics Committee in France in 2019[90] in this regard. After providing background analysis of the scientific, legal, and deontological issues raised by genome editing in humans, the Committee acknowledged that genome editing contributes to the advancement of science, even when applied in embryos, but that strict attention should be paid to the potential consequences of its use for the human germline and on the environment. It also insisted on three major points that should be further considered: (1) what will be what the impact of these technologies regarding the societal expectations (unrealistic expectations)? (2) If implementing CRISPR-Cas9 in embryos for therapeutic purposes is forbidden in France, what if it is allowed in other European countries (medical tourism)? (3) How to ensure that genome editing will be regulated only for health purposes and not for weapon development (resistance to virus or bacteria)? The Council concludes that these issues call for more information and transparency, should be opened to a wide debate with the public, and should be limited through the frame of the Bioethics Laws and the Oviedo Convention. By the end, regarding genome editing in embryos, because of the uncertainties and the risks, it recommends a cautious approach based on a possible moratorium, but surprisingly, it also recognizes that "preventing such diseases (severe and incurable) from the embryonic stage, through targeted genome repair, justifies special ethical reflection on care that may constitute a possible medical approach in the future." This position, shared by other national ethics committees,[91] is thus a step to overcome the moral debate toward possibilities to use genome editing in embryos under strict conditions in the future. Other initiatives should also be considered such as the setting up of the Association for Responsible Research and Innovation in Genome Editing[92] that shows the necessary interplay between national and international governance of genome editing. The ethics committee of Inserm is at the initiative of its creation, but its scientific committee consisted of international members. Its ambition is to promote international and interdisciplinary collaborations to foster the development of genome editing techniques embedded in a safe ethical framework as well as supporting dialogue between the various stakeholders and to provide training.

Therefore, activities on human genome editing are regulated not only by French state and EU institutions, but also by European and French organizations that represent specific communities.

DISCUSSION

Through the fragmented regulatory landscape of human genome editing at the territorial, material, and institutional levels, several interdependent determinants of regulatory fragmentation can be identified.

First, regulatory fragmentation occurs according to the remit of each organization providing norms. Such determinant is particularly emphasized by the territorial fragmentation, which is mainly based on the sharing of competences between the EU and its Member States. Such fragmentation is increased by the mobilization of various competences (for instance, the shared and complementary competences in the field of public health) linked to different objectives (for instance, good functioning of the internal market, guarantee of a high level of protection of public health) and to various legal methods (for instance, harmonization, cooperation) and legal tools with various authoritative weights (i.e., regulation, directive, guidelines). The determinant of the remit of each normative organization also arises regarding the institutional fragmentation, where various organizations gain legitimization of their normative power either from the classical democratic process (for legal institutions such as those of the EU and of the Member States) or from the communities they represent (mainly scientific communities). The remit of each normative organization is a particularly relevant determinant of the fragmentation of the human genome editing regulatory landscape given the number and variety of such organizations, which have been active in this field.

Second, the objectives that explain the normative actions are also a determinant of the fragmented human genome editing regulatory landscape as long as research, economics, public health, or bioethics objectives, for instance, are often the objects of different legal texts or at least of different rules within one legal text.

The third determinant of the fragmented human genome editing regulatory landscape relies on the various stages of development of therapy based on human genome editing techniques. Indeed, as observed in particular regarding substantive fragmentation, legal frameworks or normative recommendations target, for instance, the funding of research, clinical trials, patentability, or the marketing of medicinal products based on human genome editing techniques.

Fourth, regulatory fragmentation occurs according to the sources of human biological elements in which genome editing is conducted. Indeed, we have seen that different laws, rules, or recommendations apply to human genome editing on somatic cells and on embryonic or germ cells.

[88]http://www.academie-medecine.fr/wp-content/uploads/2016/02/Rapport-modification-du-g%C3%A8nome-27-01-16.pdf.

[89]See in addition to the National Ethics Committee that will be presented in this article, the joint communication from the INSERM Ethics Committee and the CNRS Ethics Committee on the Modification of the human germline genome by CRISPR. Serious ethical questions and condemnation following the announcement of the birth in China of genetically twins in China, December 2018; INSERM Ethics Committee Note of the Ethics Committee on the referral concerning issues related to the development of CRISPR-Cas9 technology February 2016.

[90]National Ethics Committee in France (Comité Consultatif National d'Ethique) opinion n°133 on "Ethical challenges of gene editing: between hope and caution" (2019).

[91]See *Discussion*.

[92]https://www.arrige.org/(last accessed October 2021).

Finally, the targeted population is also a determinant of the fragmented human genome editing regulatory landscape as long as the laws and the rules differ when the human genome editing techniques are to be conducted in the laboratory only for fundamental research, on clinical trials' participants, on an individual, or on numerous patients for therapy.

These determinants are very much interdependent as they often appear together in one regulatory text, although they generally imply different rules. They are part of the regulatory strategies to respond to human genome editing techniques, and as such, they contribute to the fragmentation process in order to adapt to the changing political and legal contexts. On the one hand, the process of fragmentation provides complementary rules to cover the entire field of human genome editing, such rules allowing a level of regulation (legal or normative, binding, or nonbinding) to be adapted according to territorial, institutional, or substantive aspects regarding legal, ethical, and societal implications. On the other hand, different rules from different organizations with various authoritative weights (e.g., binding or not) and the applicability of one or of several of these rules also raise legal challenges linked to potential overlapping and contradictions. Consequently, one could wonder whether the EU level or the national level of governance is the right place to pursue the regulation of human genome editing. The question may be unsolvable as both levels of governance have their own limits: the competencies limitations of the EU are salient given the cross-objectives linked to human genome editing, as well as the territorial limitations of each Member State regarding the movements across borders of persons, services, and goods including human genome editing techniques. On the opposite, the fragmentation process of the regulatory landscape allows to consider and balance various societal objectives, such as protection of fundamental rights and ethical values, protection of health, and access to safe innovative treatments, freedom of research, and competitiveness within the regulation of human genome editing. National laws and international regulations (including EU law), as well as various normative actors, are reflecting accepted social values regarding emerging technologies. Even if they are variations from one country or territory to another, the same goal is assumed in trying to balance between development and progress of science and protection of humans. While legal frameworks, such as human rights, are challenged especially regarding the emergence of human genome editing technologies (van Beers, 2020), "genome editing products could be seen as a test case for estimating the impact of legislative and nonlegislative actions, as well as investments by the EU and also as a measurement of the competences and capacity of the regulatory system."[93] In that sense, we have argued that fragmentation of the law as a dynamic process provides room for current and future solutions for more contingent responses to human genome editing reflecting the changing political, legal, and social contexts.

Nevertheless, it may be too reductive to think the regulatory landscape of human genome editing is solely fragmented as several normative activities show a tendency to provide common rules or rules as a set. For instance, the Joint Statement of Ethics Councils from France, Germany, and the United Kingdom on the Ethics of Human Heritable Genome Editing[94] follows the national positions previously adopted by these three committees in this regard[95] and provides common recommendations. It particularly shows that, despite different bioethical backgrounds, a consensus should be reached, although what is meant by "consensus" as well as how we will know it will be achieved should be clarified (Morrison and de Saille, 2019). As an introduction, the three committees recognized that their national positions were based on the core bioethical principles inherited from Beauchamp and Childress (2001) but differently balanced according to the national context and theoretical grounding. While solidarity and social justice were at the heart of the Nuffield Council of Bioethics opinion, beneficence and nonmaleficence founded one of the French and of the German ethics committees. The latter, the Deutscher Ethikrat, also built its opinion on human dignity, protection of life and its integrity, freedom, naturalness, and responsibility. Nevertheless, the three committees moved forward and assumed together that they "can conceive of cases where the clinical application of heritable genome editing could be morally permissible. We do not, therefore, consider the human germline categorically inviolable."[96] However, the councils differ on how this permissibility should be implemented and where should the limits be set.[97] As long as the core biomedical principles (beneficence, nonmaleficence, autonomy, and justice) are no longer considered as an absolute limit to use germline genome editing, and the National Councils have open room for discussions for its use in the medical interest of patients or their offspring, this position, even though not binding, could influence further revisions of the French Bioethics Law or of EU law in the future. Another example is the imaginary built into the framing of EU level legal regulation of human gene editing technologies, which is based on the tension around naturalness; safeguarding morality and ethics; and the pursuit of medical objectives for the protection of human health (Mahalatchimy et al., 2021).

[93]European Medicines Agency and Heads of Medicines Agencies. Genome editing EU-IN Horizon Scanning Report, *op. cit*. p. 10

[94]Nuffield Council on Bioethics, Deutscher Ethikrat, Comité Consultatif National d'Ethique, Joint statement on the Ethics of Human Heritable Genome Editing, March 3, 2020: https://www.ccne-ethique.fr/sites/default/files/press_release_-_heritable_genome_editing_def.pdf.

[95]Comité Consultatif National d'Éthique, Deutscher Ethikrat and Nuffield Council on Bioethics, Joint statement on the ethics of human germline interventions, March 3, 2020. https://www.ethikrat.org/fileadmin/Publikationen/Ad-hoc-Empfehlungen/englisch/joint-statement-on-the-ethics-of-heritable-human-genome-editing.pdf (last accessed June 18, 2021).

[96]Joint Statement *op. cit*.

[97]"Whilst all three reports offer reasons to conclude that the use of heritable genome editing could be acceptable to prevent the intergenerational transmission of serious hereditary disorders, the CCNE expresses a complete ethical opposition to 'enhancement' applications. The Deutscher Ethikratrecommends that the assessment of such applications should be made on a case-by-case basis. The Nuffield Council does not advocate distinguishing acceptable and unacceptable uses on a categorical basis but recognizes that judgments must take into account the interests and responsibilities of those affected in a given sociotechnical context." Joint Statement *op. cit*.

These examples highlight the defragmentation, understood as gathering together or connecting at least in some areas, may also be another characteristic of the human genome editing regulatory landscape. Therefore, both fragmentation and defragmentation may be a relevant grid of analysis to further decipher the regulatory landscape of human genome editing. Although it would require distinct research, which is not covered in this article, the French National Agency for Research–funded project I-BioLex on "fragmentation and defragmentation of the law on biomedical innovations," going beyond human genome editing, is conducting such analysis from 2021 to 2024.[98]

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AM and ER-S contributed equally to the conception, research and writing of this article. AM has worked more on the EU level regulatory landscape and ER-S more on the French level regulatory landscape. All authors contributed to manuscript revision, read, and approved the submitted version.

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