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Guest Editorial

Governing, Protecting, and Regulating the Future of Genome Editing: The Significance of ELSPI Perspectives

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1 Genome Editing Technology and Its Significance

With the recent breakthroughs in genomics and advances in genome-editing techniques, most notably the discovery of the clustered regularly interspaced short palindromic repeats (CRISPR)-associated protein 9 (Cas9),[1] the matter of

1 The discovery of Cas9 dates back to 2012, whereas the CRISPR system was discovered in 1987. *See* Y. Ishino, H. Shinagawa, K. Makino, M. Amemura and A. Nakata, 'Nucleotide Sequence of the Iap Gene, Responsible for Alkaline Phosphatase Isozyme Conversion in *Escherichia*

genome editing and health innovation has become of particular importance in society. New genome-editing techniques hold considerable potential to enhance personalized medicine and deliver cures to conditions and diseases that currently cannot be tackled. However, considerable work remains to be done in order to realize this potential.

Means to modify the human genome have been of interest to scientists for a considerable time and significant milestones were achieved during the second half of the last century.[2] Several tools have existed prior to the discovery of Cas9, such as meganucleases, zinc-finger nucleases (ZFNs), and transcription activator-like effector nucleases (TALENs).[3] Already in 2003, the first commercial gene-editing therapy — *Gendicine* — was registered in China.[4] Almost a decade later, in 2012, the first gene therapy medicinal product — *Glybera* (alipogene tiparvovec) — was approved by the European Medicines Agency for marketing within the EU.[5]

Numerous studies are being conducted to develop novel applications and therapies, as well as to improve the techniques. Although different techniques have different strengths,[6] one of the newest additions — CRISPR[7] — has several important advantages and is therefore transforming the field. It is a relatively simple and efficient technique for site-specific gene editing and obliviates

coli, and Identification of the Gene Product', *Journal of Bacteriology* 169 (1987) 5429–5433; and Y. Ishino, M. Krupovic and P. Forterre, 'History of CRISPR-Cas from Encounter with a Mysterious Repeated Sequence to Genome Editing Technology', *Journal of Bacteriology* 200 (2018) e00580-17, available online at https://journals.asm.org/doi/abs/10.1128/JB.00580-17 (accessed 31 January 2022).

The bacterial CRISPR locus was first described by F.J. Mojica, G. Juez and F. Rodriguez-Valera, 'Transcription at different salinities of Haloferax mediterranei sequences adjacent to partially modified PstI sites', *Molecular Microbiology* 9 (3) (1993) 613–621.

2 T. Friedmann, 'A Brief History of Gene Therapy', *Nature Genetics* 2 (1992) 93–98.

3 G. Silva, L. Poirot, R. Galetto, J. Smith, G. Montoya, P. Duchateau and F. Pâques, 'Meganucleases and Other Tools for Targeted Genome Engineering: Perspectives and Challenges for Gene Therapy', *Current Gene Therapy* 11 (2011) 11–27.

4 S. Pearson, H. Jia and K. Kandachi, 'China Approves First Gene Therapy', *Nature Biotechnology* 22 (2004) 3–4.

5 European Medicines Agency, *European Medicines Agency recommends first gene therapy for approval* (20 July 2021), available online at https://www.ema.europa.eu/en/news/european-medicines-agency-recommends-first-gene-therapy-approval (accessed 31 January 2022).

6 T. Gaj, C.A. Gersbach and C.F. Barbas, 'ZFN, TALEN and CRISPR/Cas-Based Methods for Genome Engineering', *Trends in Biotechnology* 31 (2013) 397–405.

7 For an overview, see K.S. Makarova and E.V. Koonin, 'Annotation and Classification of CRISPR-Cas Systems', *Methods in Molecular Biology* 1311 (2015) 47–75, and for the developments see A. Pickar-Oliver and C.A. Gersbach, 'The Next Generation of CRISPR–Cas Technologies and Applications', *Nature Reviews Molecular Cell Biology* 20 (2019) 490–507.

several important concerns connected to more traditional methods.[8] Strengths such as these position the technique as a paradigm shifter in the field.[9]

Despite the promising potential that genome editing holds, it also has limitations. For example, CRISPR-Cas9 and its follow-on techniques, like CRISPR-Cas12a, create safety concerns due to risks associated with off-target effects, impacting on any therapeutic and clinical applications of the technique.[10] There are different other techniques under development, with the aspiration to overcome such shortcomings as the CRISPR techniques demonstrate, such as prime editing and base editing. They too, have the challenge related to off-target effects but offer other advantages, such as facilitated alterations without the risk of breaking both DNA strands or using DNA templates.[11]

While there is hope that a newcomer in the field — Retron Library Recombineering (RLR) — could overcome challenges related to off-target effects, that remains to be established, along with other safety aspects.[12] Other cited limitations include a protospacer-adjacent motif requirement near the target site (which limits the regions in the genome that can be edited), as well as DNA damage toxicity and immunological response to the genome editing

8 F. Uddin, C.M. Rudin and T. Sen, 'CRISPR Gene Therapy: Applications, Limitations, and Implications for the Future', *Frontiers in Oncology* 10 (2020) DOI: 10.3389/fonc.2020.01387.

9 *Ibid.*

10 X.H. Zhang, L.Y. Tee, X.-G. Wang, Q.-S. Huang and S.-H. Yang, 'Off-Target Effects in CRISPR /Cas9-Mediated Genome Engineering', *Molecular Therapy Nucleic Acids* 4 (2015) e264. K. Murugan, A.S. Seetharam, A.J. Severin and D.G. Sashital, 'CRISPR-Cas12a Has Widespread off-Target and DsDNA-Nicking Effects', *The Journal of Biological Chemistry* 295 (2020) 5538–5553.

11 A.V. Anzalone, P.B. Randolph, J.R. Davis, A.A. Sousa, L.W. Koblan, J.M. Levy, P.J. Chen, C. Wilson, G.A. Newby, A. Raguram and D.R. Liu, 'Search-and-replace genome editing without double-strand breaks or donor DNA', *Nature* 576 (2019) 149–157. K. Saha, E.J. Sontheimer, P.J. Brooks, M.R. Dwinell, C.A. Gersbach, D.R. Liu, S.A. Murray, S.Q. Tsai, R.C. Wilson, D.G. Anderson, A. Asokan, J.F. Banfield, K.S. Bankiewicz, G. Bao, J.W.M. Bulte, N. Bursac, J.M. Campbell, D.F. Carlson, E.L. Chaikof, Z.-Y. Chen, R.H. Cheng, K.J. Clark, D.T. Curiel, J.E. Dahlman, B.E. Deverman, M.E. Dickinson, J.A. Doudna, S.C. Ekker, M.E. Emborg, G. Feng, B.S. Freedman, D.M. Gamm, G. Gao, I.C. Ghiran, P.M. Glazer, S. Gong, J.D. Heaney, J.D. Hennebold, J.T. Hinson, A. Khvorova, S. Kiani, W.R. Lagor, K.S. Lam, K.W. Leong, J.E. Levine, J.A. Lewis, C.M. Lutz, D.H. Ly, S. Maragh, P.B. McCray Jr, T.C. McDevitt, O. Mirochnitchenko, R. Morizane, N. Murthy, R.S. Prather, J.A. Ronald, S. Roy, S. Roy, V. Sabbisetti, W.M. Saltzman, P.J. Santangelo, D.J. Segal, M. Shimoyama, M.C. Skala, A.F. Tarantal, J.C. Tilton, G.A. Truskey, M. Vandsburger, J.K. Watts, K.D. Wells, S.A. Wolfe, Q. Xu, W. Xue, G. Yi, J. Zhou and The SCGE Consortium, 'The NIH Somatic Cell Genome Editing program', *Nature* 592 (2021) 195–204.

12 Wyss Institute, *Move over CRISPR, the retrons are coming* (30 April 2021), available online at https://wyss.harvard.edu/news/move-over-crispr-the-retrons-are-coming/ (accessed 31 January 2022).

system.[13] Overcoming these limitations is central to ensuring precise, safe and effective genome editing and realizing the potential that the technique holds.[14] These practical limitations would suggest that genome editing is still in its infancy.[15]

2 Genome Editing, Health Innovation, and Responsible Regulation

The potential of genome editing in transforming personalized medicine is only one side of the coin. In principle, the techniques may be used to target virtually any part of the human genome, and thus their potential application is not limited to strictly health-related interventions, such as repairing, modulating, replacing, or adding gene(s) in order to prevent or cure genetic diseases. Acknowledging that there could be cases where the line between health-related and non-health-related interventions is thin, there could also be cases where concerns emerge over improving skills or performances (enhancement). Moreover, genome editing can be used on germline cells, not only somatic ones — thus, in the latter instance, irreversibly altering the genome of future descendants and raising concerns on the protection of the human genome as the common cultural heritage of humanity.[16]

The power of shaping the future of humanity that genome editing holds and the potential to do that at an unprecedented level and scale creates several considerable questions and concerns. The misuse of technology has been a significant concern in biology and medicine since the horrific Nazi experiments and equally abhorrent underlining eugenics ideology came to light. Humanity's need to ensure that such atrocities would never be possible again has informed the European legal standards in the field. Without denying the need to develop solutions to effectively prevent misuse of the technology, it is now clear that a blanket ban on germline interventions as such could deprive patients and future children of a possibility to benefit from scientific advances in the field of preventive and curative medicine.

13 Uddin et al., *supra* note 8.

14 *Ibid.*

15 H. Li, Y. Yang, W. Hong, M. Huang, M. Wu and X. Zhao, 'Applications of Genome Editing Technology in the Targeted Therapy of Human Diseases: Mechanisms, Advances and Prospects', *Signal Transduction and Targeted Therapy* 5 (2020) 1.

16 UNESCO, *Universal Declaration on the Human Genome and Human Rights* (11 November 1997), available online at http://portal.unesco.org/en/ev.php-URL_ID=13177&URL_DO=DO_TOPIC&URL_SECTION=201.html (accessed 31 January 2022), Article 1.

The design of the European regional legal standards pertaining to genome editing dates back to 1997, when the Council of Europe Biomedicine Convention was adopted,[17] and 2001, when the EU Clinical Trials Directive was adopted.[18] Both these dates fall before the registration of the first gene therapy medicinal product. The Biomedicine Convention prohibits deliberate heritable changes to the human genome, as well as non-health-related applications.[19] The EU clinical trials framework contains a similar norm vis-à-vis clinical trials.[20]

Since then, the European legal framework has become slightly more nuanced, covering the requirements for bringing gene therapy products on the market within the EU,[21] as well as preventing certain biotechnology applications from being patentable due to incompatibility with morality under the EU Biotechnology Directive.[22] Common to these legal frameworks is the fact that they were crafted and adopted prior to the discovery of the newcomers in the genome-editing toolbox, prior to the successful attempt to apply genome-editing techniques to human embryos in 2015,[23] and prior to the attempt to introduce heritable changes during the course of an *in vitro* fertilization procedure in 2018.[24] Thus, the European legal responses were largely shaped for the future, against the background of a picture, painted in broad strokes, of

17 Council of Europe, *The Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine* (*ETS No 164*) (4 April 1997), Article 13.

18 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, OJ L 121, 1 May 2001, pp. 34–44, Article 9.6.

19 Biomedicine Convention, *supra* note 18, Article 13.

20 Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC Text with EEA relevance OJ L 158, 27 May 2014, pp. 1–76, Article 90.

21 Advanced therapy medicinal products merited a special legal framework in 2007, Regulation (EC) No 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) No 726/2004 (Text with EEA relevance) OJ L 324, 10 December 2007, pp. 121–137.

22 Directive 98/44/EC of the European Parliament and of the Council of 6 July 1998 on the legal protection of biotechnological inventions OJ L 213, 30 July 1998, pp. 13–21, Article 6.2.b.

23 P. Liang, Y. Xu, X. Zhang, C. Ding, R. Huang, Z. Zhang, J. Lv, X. Xie, Y. Chen, Y. Li, Y. Sun, Y. Bai, S. Zhou, W. Ma, C. Zhou and J. Huang, 'CRISPR/Cas9-Mediated Gene Editing in Human Tripronuclear Zygotes' *Protein & Cell* 6 (2015) 363372.

24 S. Krimsky, 'Ten ways in which He Jiankui violated ethics', *Nature Biotechnology* 37 (2019) 19–20.

what potential the technology held, the challenges it might bring, and how they should be balanced against each other.

Already in 1998, soon after the Biomedicine Convention was adopted, some critical remarks were made on the limitations to scientific advances that Article 13 prescribed. For example, Abbing noted that "[i]n as far as this [Article 13] is inspired by moral conservatism only, it stands in the way of an appropriate dynamic approach to human rights and health."[25] Since then, the criticism has been piling up. Some have called for removing obstacles to realize the full potential that the technology offers, arguing that harms could be tackled through remedies to victims of violations in specific cases.[26] Others have suggested such an approach would be morally reckless, calling for the establishment of clear avenues for further work from ethical, legal, social, and technical perspectives to prepare foundations for revisiting the current regulatory approach.[27]

Recent advances and occurrences have triggered intense debates on interventions in the human genome among scientists, lawmakers, and policymakers at multiple levels. To illustrate, the American National Academy of Sciences, the American National Academy of Medicine, the Chinese Academy of Sciences, and the Royal Society of the UK organized an International Summit in Washington, DC, USA in December 2015. They released an International Summit Statement emphasizing that "it would be irresponsible to proceed with any clinical use of germline editing unless and until (i) the relevant safety and efficacy issues have been resolved, based on appropriate understanding and balancing of risks, potential benefits, and alternatives, and (ii) there is broad societal consensus about the appropriateness of the proposed application."[28] Similarly, in 2018, the International Bioethics Committee under the Universal Declaration on the Human Genome and Human Rights (1997) called for a "moratorium on genome engineering of the human germline,

25 H.D.C. Roscam Abbing, 'The Convention on Human Rights and Biomedicine: An Appraisal of the Council of Europe Convention', *European Journal of Health Law* 5 (1998) 377–387.

26 A. Boggio and C.P.R. Romano, 'Freedom of Research and the Right to Science: From Theory to Advocacy', in: S. Giordano, J. Harris and L. Piccirillo (eds.), *The Freedom of Scientific Research: Bridging the Gap between Science and Society* (Manchester: Manchester University Press, 2018), pp. 162–175.

27 In regard to the Swedish national context, see S. Slokenberga and H.C. Howard, 'The Right to Science and Human Germline Gene Editing. Sweden, Its External Commitments and the Ambiguous National Responses under the Genetic Integrity Act', *Förvaltningsrättslig Tidskrift* 2 (2019) 199–222.

28 The National Academies of Sciences, Engineering, and Medicine, *On Human Gene Editing: International Summit Statement* (3 December 2015), available online at https://www.nationalacademies.org/news/2015/12/on-human-gene-editing-international-summit-statement (accessed 31 January 2022).

at least as long as the safety and efficacy of the procedures are not adequately proven as treatments."[29]

In 2021, the WHO issued Recommendations on Human Genome Editing for the Advancement of Public Health (2021) with the aspiration to set global standards for governance and oversight of human genome editing,[30] as well as recommendations on the issues related to genome editing.[31] Both these documents provide advice and recommendations on governance mechanisms for human genome editing at various regulatory levels.[32] The matter has also received attention from the Council of Europe and the EU, triggering a report on the Ethics of Human Genome Editing in 2021.[33] It has been on the agenda since at least 2015, but only modest action has followed thus far. In 2015, the HD BIO stated that it "agrees, as part of its mandate, to examine the ethical and legal challenges raised by these emerging genome editing technologies, in the light of the principles laid down in the Oviedo Convention."[34] In 2018, it emphasized that "ethics and human rights must guide any use of genome editing technologies in human beings,"[35] and included in its action plan for 2020–2025 the ambition to either clarify or revise the Biomedicine Convention. In 2021, a communiqué was released noting that some clarifications are to be expected, but no revision of the Biomedicine Convention is currently on the agenda of the HD BIO.[36]

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29 UNESCO, Report of the IBC on updating its reflection on the Human Genome and Human Rights (2 October 2015), available online at https://unesdoc.unesco.org/ark:/48223/pf0000233258 (accessed 31 January 2022), p. 3.

30 World Health Organization, *Human genome editing: recommendations* (12 July 2021), available online at https://www.who.int/publications/i/item/9789240030381 (accessed 31 January 2022).

31 *Ibid*.

32 A summary is available in the position paper by the World Health Organization, *Human genome editing: position paper* (12 July 2021), available online at https://www.who.int/publications/i/item/9789240030404 (accessed 31 January 2022).

33 European Group on Ethics in Science and New Technologies, *Ethics of Genome Editing* (March 2021), available online at https://ec.europa.eu/info/sites/default/files/research_and_innovation/ege/ege_ethics_of_genome_editing-opinion_publication.pdf (accessed 31 January 2022).

34 Committee on Bioethics (DH-BIO), 8th meeting, 1–4 December 2015 Strasbourg, Statement on genome editing technologies, DH-BIO/INF (2015) 13 FINAL, p. 2.

35 Statement by the Council of Europe Committee on Bioethics, *Ethics and Human Rights must guide any use of genome editing technologies in human beings*, available online at https://www.coe.int/en/web/portal/-/-ethics-and-human-rights-must-guide-any-use-of-genome-editing-technologies-in-human-beings (accessed 29 March 2022).

36 Genome editing technologies: some clarifications but no revision of the Oviedo Convention, available online https://www.coe.int/en/web/bioethics/-/genome-editing-technologies-some-clarifications-but-no-revision-of-the-provisions-of-the-oviedo-convention (accessed 29 March 2022).

3 Genome Editing, a Stress Test for Biomedical Regulation

It is clear that the advances and the potential that genome-editing techniques holds for a myriad of possible applications present a stress test to the existing legal frameworks, going beyond the question of germline interventions. They require scrutiny and revisiting of the foundations that the current legal frameworks rest upon and possible ways forward, accounting for not only the legal concerns, but also the ethical and social concerns that emerge. In tackling the multi-faceted problems related to human genome editing, the human rights pillars that the European legal frameworks in biomedicine and governance of medicinal products rest upon are of importance, as are market-related and property rights-related aspects. Several scholars have highlighted the rapidly developing intellectual property (IP) landscape, and the significant role that not only the IP and patent systems, but also competition law, may play for the governance of genome editing.[37] These legal areas play a central role not only in promoting research and development, but also in in enabling and governing the realization of rights such as the availability and accessibility of gene editing therapies in healthcare.[38]

On 3–4 November 2021, the Nordic Permed Law network held a symposium on "Genome Editing, Health innovation, and Responsible Regulation," speakers, respondents and participants gathered to examine in greater detail the regulation of health innovation in the area of genome editing, illustrate the challenges and illuminate the possible policy avenues forward. This special issue is prepared in connection to the Symposium and with the extensive support of the European Journal of Health law team, in particular, Professor H. Nys. The goal of this issue is to shed light on the evolving debates, with a specific focus on interdisciplinary and legal perspectives and with a keen eye on elucidating challenges and opportunities of appropriate technology governance. Key questions that shape this contribution are how the scientific advances challenge the existing legal solutions and values underpinning them, and how the law could and should respond to genome editing and health innovation in order to adequately reconcile the different competing interests at stake and enhance

37 S. Parthasarathy, 'Use the Patent System to Regulate Gene Editing', Nature 486 (562) (2018); A. Shukla-Jones, S. Friedrichs and D.E. Winickoff, 'Gene Editing in an International Context: Scientific, Economic and Social Issues across Sectors', *OECD Science, Technology and Industry Working Papers* (2018).

38 Cf., D. Matthews, A. Brown, E. Gambini, T. Minssen, A. Nordberg, J.S. Sherkow, J. Wested, E. van Zimmeren and A. McMahon, The Role of Patents and Licensing in the Governance of Human Genome Editing: A White Paper (30 July 2021). *Queen Mary Law Research Paper No. 364/2021*, Available online at https://ssrn.com/abstract=3896308.

personalized medicine. This special issue has two parts. Part I explores general ethical, legal, social and policy implications of genome editing technologies. Part II continues this analysis now focusing on bringing genome editing to the market and making it available to patients and addressing genome editing technology regulation through procedures for regulatory approval, patent law and competing law.

4 Part I: A Roadmap of ELSPI Perspectives

Judit Sándor, with the contribution "Genome editing: Learning from its past and envisioning its future," offers a sophisticated scholarly insight into the fundamental milestones that are of key importance to the present technology and applications in the field of genome editing, with a particular focus on ethical and legal distinctions between somatic and germline interventions. Sándor examines ethical violations, such as the case of Dr. He Jankui, and describes the profound legal and ethical questions that such interventions raise and challenges to the fundamental concepts of medical law ethics and law and the existing legal frameworks in the field. Sándor highlights the need to "learn from the past episodes of eugenics and the instances of fraud and failure that have been the result of merciless scientific competition, unfettered commercial interest, or simply individual pride" and underscores human rights lawyers' responsibility to engage in discussions regarding the societal concerns that biotechnology creates.

New genome-editing techniques, such as CRISPR, can be of tremendous value for advancing and transforming medical care. Anne Kjersti Befring, in her contribution "Transformation of medical care through gene therapy and human rights to life and health — Balancing risks and benefits," examines how the right to health and life could shape regulations relating to access to gene therapy. Befring alerts readers to the need for common standards in international regulations, cooperation between countries and between public health services and commercial entities, in order to continue scientific development in the field and ensure fair access to therapies.

Artificial intelligence has been presented as a powerful tool in the field of genome therapy. While these two fields have several commonalities, such as their cutting-edge nature and capacity to transform society, they trigger different legal frameworks that are not sufficiently linked for regulating use of the technologies together. Anastasiya Kiseleva, in "Somatic genome editing with the use of AI: Big promises but doubled legal issues," examines the legal issues related to the use of AI in somatic genome editing and suggests some possible

solutions. Kiseleva sheds light on the requirements and interplay of these frameworks, and argues that management of common risks is only possible through common procedures. Concrete measures need to be taken in order for effective procedures to be established.

Genome editing can be perceived not only as a tool to further the right to health and life, but also as a means that contributes to the realization of the right to habilitation under Article 26 of the Convention of the Rights of Persons with Disabilities. Pin Lean Lau, in "Addressing cognitive vulnerabilities through genome & epigenome editing: Techno-legal adaptations for persons with intellectual disabilities" examines how persons with disabilities may access the benefits that genome editing may offer, without compromising other rights and principles. Lau argues for the need for a paradigm shift in disability studies discourse, so that persons with disabilities are not excluded from the scientific advances that genome editing technology could offer.

Human rights have played a tremendous role in shaping the regulation of new health technologies.[39] In European legal fora, the interpretations provided by the European Court of Human Rights, which shape national laws and practices, have been of particular importance. Human germline genome editing is not an exception. While the Court has not had a chance to adjudicate on the question of genome editing yet, when the occasion comes, the point of departure will be the ECHR, the European human rights catalogue — and the interpretation of these norms given by the Court on different occasions. Merel M. Spaander, in her contribution "The European Court of Human Rights and the emergence of human germline genome editing — 'The right to life' and 'The right to (artificial) procreation'," examines how the existing human rights interpretations could shape legal responses to human germline gene editing. Spaander shows that there is a tendency for the Court to extend the reproductive rights involving various reproductive technologies, but at the same time leave scope for member states to prescribe limitations. While germline gene editing could logically fall within the scope of protection of private life, the Court's openness to granting a wide margin of appreciation on matters pertaining to human dignity could be debated.

Currently, the European legal fora in the area of human germline gene editing are characterized by bans set forth in regional and national legal instruments. The creation of a possibility to enhance the reproductive rights of persons suffering from some genetic conditions would argue for removing the bans. Consequently, under this argument, the permissible applications would

39 See M.L. Flear, A.-M. Farrell, T.K. Hervey and T. Murphy (eds.), *European Law and New Health Technologies* (Oxford: Oxford University Press, 2013).

be rather limited. This has led to some questioning on whether limited application justifies the investment of public resources in order that the technology can be developed. Noemi Conditi agrees that when safety is no longer a concern, regulation may become a necessity. In her contribution "Regulating heritable human genome editing: Drawing the line between legitimate and controversial use," Conditi argues for introduction of a new threshold — accessibility to germline gene-editing technology for genetic conditions for which preimplantation genetic diagnosis is available. This threshold, in the author's opinion, avoids the controversies surrounding the concepts of health and disease and offers a possibility to shape harmonious national frameworks on technology governance.

5 Part II: Bringing Genome Editing to the Market and Making It Available to Patients

The EU regulation on advanced therapy medicinal products is a key legal act shaping the detailed requirements for bringing gene therapy products to the market. However, under certain circumstances, gene therapy interventions can be lawfully applied in healthcare without having received the necessary approvals. Vera Lucia Raposo, in "A room with a view (and with a gene therapy drug): Gene therapy medicinal products and genetic tourism in Europe," examines the existing flexibilities for early access to medicinal products in the EU legal framework, and points at legal weaknesses in these mechanisms that risk compromising patient safety. Thus, Raposo indicates a need for better information management and controls, as means to enable responsible governance of the early use of somatic gene therapy for patients in need.

An additional challenge is that the regulatory framework in EU member states is fragmented between norms of international law, secondary EU law, and national legislation. Focusing on the "precautionary principle," which has often provided the basis for legislation, the contribution by Michal Koščík and Eliška Vladíková explores this challenge and analyzes the "The object-based and process-based regulation of genome editing." The authors ask "whether the wider regulatory framework applicable to the member states of the EU contains suitable tools to react to the rapid advances in science, especially as to the question of germline editing technologies." They arrive at the conclusion "that the EU framework for advanced treatments and medicinal products is in a state where it can, in principle, address the questions associated with the safety and efficacy of germline editing technologies." However, the authors also argue that the expanding knowledge in the field creates the need to replace

current regulations, which are based on the lack of knowledge (such as precautionary moratoria), with regulations that are based on actual knowledge (such as risk-based regulation).

Eventually, when germline gene editing is considered relatively safe (shows a positive risk-benefit ratio), safety-related concerns will cease to function as arguments to uphold bans. Morality-based arguments will remain, which would allow countries and regional legal orders freedom in rethinking the bans. Putting aside the difficult question of whether to allow human germline gene editing, Santa Slokenberga, in her contribution "What would it take to enable germline editing in Europe for medical purposes?," examines the possibility of lifting the two bans shaping the European legal environment. Slokenberga argues that while neither ban is set in stone, a considerable level of agreement between stakeholders representing diverse groups will be needed. Moreover, she shows that willingness *per se* will not be sufficient; the substantive preconditions prescribed by each of the respective legal orders will need to be satisfied. This points at the need for a more sophisticated legal debate, focusing on key principles underpinning existing legal frameworks and shaping the practice of medicine.

Lastly, the full realization of the benefits that human genome editing technology promises society also requires that rules that directly or indirectly regulate the ownership and dissemination of the technology are adequate to promote its further innovation, development, and dissemination. In particular, patent law plays an important role, by balancing the rewards granted to those who have researched and developed key patent-protected human genome editing technology against the interest of securing access to the technology for those who may engage in further research and follow-on innovation. Rules regarding, e.g., research exemptions to the exclusivity of patent rights are crucial in protecting further research and development, while such exemptions cannot be made so broad as to discourage investments into pioneer technology and to encourage free-riding upon other market actors' investments into innovation.

Oliver Feeney, contributes to this discussion with a legal sociological perspective in "Genetics and Justice, Non-ideal theory and the role of Patents: the case of CRISPR-Cas9." The starting point of this article is that there are ongoing concerns of social justice regarding inequalities in the distribution of access to potential genome editing technologies, and the prior work by Colin Farrelly within non-ideal theory, which advances a justification for the use of patents to speed up the arrival of safe and effective interventions for all, including the socially disadvantaged. Feeney argues that such success is less assured when one considers the actual functioning of patents and the practical

implications of the patent system in the context of biotechnological innovations. Arguing also that non-ideal theoretical approaches risk reverting back to a form of ideal theory if they simply refer to such real-world constraints — e.g. patents — but do not critically assess and fully examine how such constraints manifest themselves in practice. The author highlights important considerations to develop and foster a more robust non-ideal approach to justice in biotechnological developments.

Continuing the discussion on patent rights, Duncan Matthews, Timo Minssen and Ana Nordberg analyse the role that '*ordre public*' and morality exceptions can play in the granting of patents on inventions in the field of human germline editing and the consequences of such policy option. This piece offers a contextual overview of the current patent landscape and related patent disputes and, proceeds with a brief analysis of 'ordre public' and morality exceptions under patent law in international, national and regional law, and their implications for innovation and access to novel treatments. The authors argue that patent exceptions should not be used as a blunt policy instrument, nor interpreted in a way that is contrary to the patent system's overall objectives. Consequentially, in the context of human germline editing, 'ordre public' and morality-based exceptions should be interpreted and applied in a way which allows providing an incentive to health innovation with the protection of societal higher normative values. The authors further emphasise the need to base regulatory decisions on a sound understanding of both the underlying science as well as the broader ethical, social and legal implications. Thinking about the future, the authors propose and outline further analysis and debate as to the role that patent law can play in the context of genome editing technologies.

Dissemination of human genome editing technology is also essential in order for the technology to be developed into commercial applications that will reach and benefit end consumers, such as specific disease treatments. In this endeavor, collaborations between the technology holder and other market actors are crucial. In this context, competition law may limit the methods for collaboration, as certain types of collaborations which involve the licensing of patent rights may restrict competition. Vladimir Bastidas Venegas argues, in his contribution "The application of EU competition law to the exploitation of human genome editing technology," that there are a number of uncertainties in the competition law regime regarding the assessment of patent pools as well as surrogate, exclusive, and ethical licensing arrangements, which are important methods for disseminating key technologies in the sector. Such uncertainties may have the effect of discouraging market actors from applying methods of collaboration that may be illegal under competition law, while promoting

other types of collaborations that are less adapted to the needs of technology holders and potential users. All in all, this may have a negative effect on the dissemination of human genome editing technology. While competition law has the important role to protect a minimum level of competition in innovation and in markets for the commercial application of human genome editing technology, there is also a risk that the obstruction of effective dissemination may reduce or delay some of the benefits to society provided by this cutting-edge technology.

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