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Towards an ethical framework for genome editing

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Technologies for genome editing with arcane names such as CRISPR appear to present unexpected possibilities for biotechnological applications. But these possibilities have generated much debate about the ethical, legal and societal implications of the new genome editing techniques. While some associate their use with risks and dangers that far exceed those of conventional methods of genetic engineering, others emphasize the enormous possibilities—in particular of CRISPR as it is cheaper and more easy to use than TALEN or ZNFs—to develop tools and applications that can help to address urgent societal challenges.

> *"... the decisive challenging point of genome editing is not necessarily the question of how to apply it, but the inherent vagueness that comes with any application."*

Emerging genome editing technologies such as CRISPR are not only necessary for progress in basic research, but are also to solve social or environmental problems. Yet, there is an inherent tension in this assumption based on how one defines "emerging technologies". The most simple definition would conceptualize novel biotechnologies as the application of expert knowledge to achieve practical goals. But there are at least two problems with this definition.

First, it implies that the end use of a technological invention could be known in advance, and that its risks and benefits can be assessed *a priori* [1]. In some cases, however, risks and problems, which were thought to be under control, turned out to be more challenging, as in the case of Golden Rice, which recently experienced unexpected difficulties. In other cases, new methods—such as sequencing technologies—not only revolutionized research, but also created unforeseen and unanticipated opportunities for clinical applications.

Second, a major lesson of the past two decades is that undeniable vagueness remains even in terms of particular applications of biotechnology. Nobody could know in advance if the aims of a given project will be achieved, but, much more importantly, if the potential solutions to identified societal needs will be societally recognized as suitable and the associated risks as acceptable. Against this background, potential uses of CRISPR start with the question of which application would be more or less urgent. The UK Nuffield Council on Bioethics identifies the application of genome editing to the fields of human reproduction and livestock breeding as the two issues with the most urgent need for ethical consideration, whereas the US National Academies of Sciences, Engineering, and Medicine (NAS) consider therapeutic and clinical, environmental, agricultural and basic research issues as equally important.

With that said, we argue that the decisive challenging point of genome editing is not necessarily the question of how to apply it, but the inherent vagueness that comes with any application. This vagueness comes from an uncertainty of current regulatory regimes, an ambivalent trust in institutions and a fragile openness within the framework of Responsible Research and Innovation (RRI). In order to resolve this vagueness, we discuss the precautionary principle as a sensitive and innovation-driven approach for discussing the applications of CRISPR.

Regulatory uncertainty

Whether as a research tool to alter specific genes or to engineer animal modes or as a tool to develop new therapies or plant varieties, precision genome editing is a subtle and yet disruptive technology. The reason why CRISPR has such a disruptive potential is not that it is per se more dangerous or offers more possibilities than other technologies. But, it has greatly increased the speed of research and developments, which challenges regulatory regimes even if many of these challenges have already been addressed in regard to other technologies. Furthermore, CRISPR itself is a good example of how the distinction between basic research and application-driven research is getting blurred. The technology emerged from many years of basic research to understand bacterial immunity against viral infections; when its potential for genome editing was discovered, CRISPR rapidly became an important tool in many research and application contexts.

> *"... the therapeutic application of CRISPR in human medicine requires clear divisions between the context of research, the context of therapy and the context of reproduction."*

Nevertheless, regulation frameworks have to be built on reliable and precise distinctions. By way of example, the therapeutic application of CRISPR in human medicine requires clear divisions between the context of research, the context of therapy and the context of reproduction. While it is necessary to proceed with research and to develop new

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therapeutic approaches, the use of genetically modified cells in reproductive contexts is highly controversial [2]. But, even despite a broad consensus—backed by the Oviedo Convention as well as by nearly all scientific and political institutions—not to pass this line, this agreement has recently come under pressure in light of new developments [3] and institutional statements. The US National Academies of Science argue for an important shift of future regulation as they switch from "not allowed as long as the risks have not been clarified" into "allowed if the risks can be assessed more reliably". It could be interpreted as if the US academies are no longer advocating a partially fundamental, partially risk-related rejection of germline therapy by genome editing, but a general permission guided by formal and material criteria.

"... trust in institutions and regulatory structures is a blank check by which the public gives them credit to act in their best interest when dealing with novel and unpredictable situations."

The second regulatory uncertainty is connected to the security and safety implications of both the unintended or purposeful misuse of CRISPR. This aspect has especially been addressed in the 2016 report of the US President's Council of Advisors on Science and Technology, where genome editing techniques and especially CRISPR were classified as a potential tool to develop weapons of mass destruction. Nevertheless, there is still a structural problem: Research in this field moves so fast that regulatory and control regimes, such as the Biological Weapons Convention, cannot keep up with the speed of development. Thus, despite the need for institution-based safety regimes, the development of this safety culture—for and with all those researching on and with CRISPR—will be a regulatory bottleneck for future developments.

A field in which the societal and regulatory modes of deliberation are perhaps challenged most is the use of CRISPR in agriculture to develop new plant varieties. In product-based regulation, which is practised in the United States, certain modifications—for example, a species-specific point mutation to increase resistance against a fungal disease that does not change the phenotype beyond the species' natural variation—would not be considered relevant for risk assessment. However, if the procedure is central to regulation, as is the case in the EU, any point mutations inserted with CRISPR will be classified as genetic modification and thus subject to risk assessment and regulatory control.

While the European Commission is still debating whether and how to regulate the application of genome editing in agriculture, two parallel developments speed up the debate. First, after non-governmental organizations and trade unions called on the French government to regulate organisms created through all methods of mutagenesis, including classical ones, France referred the case to the European Court of Justice. While the court's decision can be expected in 2018 at the earliest, the problem is exacerbated by the fact that the use of CRISPR has already contributed to new plant varieties that are ready for field trials [4].

A further development which has to be considered is the increasing concern that regulatory ambiguity is a problem for all actors, including the scientific community, and entails massive financial consequences. This is especially the case in the EU, and to some extent in the United States, as long as politicians and regulatory agencies are still debating how and to which extend plant varieties created through genome editing should be regulated. In the meantime, other countries are ploughing ahead: Sweden decided in 2015 and the Netherlands in February 2017, that the technical and legal arguments in favour of non-regulating genome editing were sufficient and told their plant scientists to go ahead. Although Sweden stated that it would adhere to EU-wide regulations once the EC decides on how to regulate genome editing, it may affect research and development programmes and the countries' investments into these.

Ambivalent trust in institutions

The future development of CRISPR not only depends on clear and efficient regulatory frameworks, but also on scientific and governmental institutions that are able to keep up with the pace of research and technological advances and that can provide guidance and orientation. Such institutions—whether individual research institutes, hospitals or complex structures such as a public health system or the regulatory system for drug approvals—are socially embedded frameworks that can empower societies and individuals by ensuring stable operating environments, predictable decision-making and the ability to deal with problems and unexpected situations. In this sense, institutions could be described as trusted gatekeepers in dealing with emerging biotechnologies. Based on the experience that such institutional structures guarantee the safety of drugs or the safety of food, most citizens trust institutionalized rules, responsibilities, norms and authorities. In short, trust in institutions and regulatory structures is a blank check by which the public gives them credit to act in their best interest when dealing with novel and unpredictable situations.

Yet, in the context of biotechnology, this notion of institutional responsibilities and the trust put in them has been challenged as the standing of institutions with significant systemic influence has declined, but also as it has become more difficult to draw consistent lines between public and private interests. CRISPR is actually a good example to illustrate this increasing confluence of different actors and interests. For instance, one of the first human clinical trials for cancer immune therapy that uses genome editing to modify the patient's T cells is carried out by a public institution, but with private funding [5]. The crucial point is not whether scientific institutions have economic interests in their research. Instead, the question is whether institutional frameworks are still trusted to act in the public interest despite the influx of private money or financial incentives.

"... openness means that different interests are handled transparently and given equal weight"

It was therefore an important message that some of the inventors of CRISPR guarantee academics free access to CRISPR tools through Addgene, a non-profit organization. At the same time, the institutions that control the IP for CRISPR have sublicensed their patents for specific genes and whole applications to surrogate companies [6]. Eventually, this could change the current patenting situation from a non-exclusive access and a partially open approach to a more or less exclusive situation, defer research into socially valuable but unprofitable applications, and create a bottleneck for future innovation in general.

Box: Further reading

Institutional statements on genome editing

German Ethics Council (2017) Germline intervention in the human embryo: German Ethics Council calls for global political debate and international regulation. http://www.ethikrat.org/files/recommendation-germline-intervention-in-the-human-embryo.pdf [Accessed 30 September 2017]

National Academies of Sciences, Engineering, and Medicine (2016) *Gene drives on the horizon: advancing science, navigating uncertainty, and aligning research with public values*. The National Academies Press, https://doi.org/10.17226/23405

National Academies of Sciences, Engineering, and Medicine (2017) *Human Genome Editing: Science, Ethics, and Governance*. The National Academies Press, https://doi.org/10.17226/24623

Nuffield Council on Bioethics (2016) Genome editing: an ethical review. http://nuffieldbioethics.org/wp-content/uploads/Genome-editing-an-ethical-review.pdf [Accessed 30 September 2017]

President's Council of Advisors on Science and Technology (2016) Letter Report on Action Needed to Protect against Biological Attack. https://obamawhitehouse.archives.gov/sites/default/files/microsites/ostp/PCAST/pcast_biodefense_letter_report_final.pdf [Accessed 30 September 2017]

Applications of genome editing

Bollinedi H, Gopalakrishnan S, Prabhu KV, Singh NK, Mishra S, Khurana JP, Singh AK (2017) Molecular and functional characterization of GR2-R1 event based backcross derived lines of golden rice in the genetic background of a mega rice variety swarna. *PLoS One* 12: e0169600

Kaiser J (2017) U.S. panel gives yellow light to human embryo editing. *Science*, https://doi.org/10.1126/science.aal0750

Waltz E (2016a) CRISPR-edited crops free to enter market, skip regulation. *Nat Biotechnol* 34: 582

Waltz E (2016b) Gene-edited CRISPR mushroom escapes US regulation. *Nature* 532: 293

Ethical criteria for genome editing

Kaebnick GE, Heitman E, Collins JP, Delborne JA, Landis WG, Sawyer K, Taneyhill LA, Winickoff DE (2016) Precaution and governance of emerging technologies. *Science* 354: 710–711

Parke EC, Bedau MA (2009) The precautionary principle and its critics. In *The ethics of protocells. Moral and social implications of creating life in the laboratory*, Bedau MA, Parke EC (eds), 69–88. MIT Press

Reber B (2017) RRI as the inheritor of deliberative democracy and the precautionary principle. *J Responsible Innov*, 1–27, https://doi.org/10.1080/23299460.2017.1331097

Socio-economic and patenting issues

Contreras JL, Sherkow JS (2017) Patent pools for CRISPR technology-Response. *Science* 355: 1274–1275

Sherkow JS (2015) Law, history and lessons in the CRISPR patent conflict. *Nat Biotechnol* 33: 256–257

Sherkow JS (2016) CRISPR: Pursuit of profit poisons collaboration. *Nature* 532: 172–173

Wesseler J, Zilberman D (2014) The economic power of the Golden Rice opposition. *Environ Dev Econ* 19: 724–742

Furthermore, the current institutional framework and the trust invested into it is challenged by another development: While institutions are more or less locally and nationally embedded, scientific research is a global endeavour, and other countries or regions may have different interests, regulations and research agendas. At the same time, the national institutional settings are currently trying to respond on their respective local area. Another example of how CRISPR challenges institutional frameworks in a global context is its use to modify human embryos. While the scientific community in Western countries agreed not to pursue this line of research, Chinese researchers eventually published the results of experiments to correct a gene defect in human embryos. Since then, US scientists have also applied genome editing to human embryos, and the NAS now recommend research to explore the application of genome editing in the context of reproduction. The decisive point is not whether or not the underlying rationale for this recommendation has been right or not, but that it has been changed without an intense deliberative process that involves all actors [7].

Openness within responsible research and innovation

Although concepts such as Responsible Research and Innovation (RRI) and Responsible Innovation (RI) put a strong—albeit uncritical—emphasis on open-mindedness, openness itself is an ambiguous term and it does not equate to having no individual interests. Furthermore, there are not only blurred lines between publicly and privately funded research, but also between scientific evidence and so-called alternative facts, which exacerbate the question of who—or which institution—has sufficient public trust to provide guidance and orientation for research. In this context, openness means that different interests are handled transparently and given equal weight. This is also the crucial point regarding the current debate about patent rights. Open-mindedness in this case does not mean that economic interests are inherently problematic, but in the case they are not handled transparently and non-exclusive they could lead to societal mistrust and negative perception of a whole technology [8].

Real open-mindedness at this point means that science must be open to addressing societal needs in an open and transparent discussion. Vice versa, there is a growing societal interest not only in the results of research, but also in setting research agendas and processes [9]. At the same time, the ideal image of public participation has begun to crack: Ethical reflections remain without effect unless corresponding criteria for accepting or rejecting a particular application or use of a new technology are developed.

Reframing a precautionary-based approach

Confronted with this vagueness inherent of emerging biotechnologies such as genome editing, a more or less precautionary-based approach is prudent, and indeed comprises important elements for a framework of

responsible decision-making in dealing with new biotechnologies. However, while the precautionary principle was in fact established to provide guidance for situations in which a new technology might pose risks to human health or the environment, it has become subject to systematic critique arguing that it has become a reactionary stop sign ethics, and that all significant aspects are already addressed by institution-based regulatory risk assessment [10,11].

When addressing this argument, it is important to distinguish between risk assessment and a precautionary-based approach. The idea of risk assessment is to provide a mechanism for balancing risks and benefits when the risks are clearly defined and quantifiable. But, there are general limitations, especially when dealing with emerging biotechnologies in the first stages of development, as it is the case for CRISPR. This is due to the inherent fluid boundaries, possible fields of application, and the unknown and extremely dynamic future developments of this technology. Thus, the uncertainty, ambiguity and openness of emerging biotechnologies create a need to distinguish between risk assessment and a precautionary approach.

> *"It lies within the precautionary principle that precaution and innovation cannot be framed as opposing and mutually exclusive poles"*

Second, the core characteristic of the precautionary-based approach is that it must not conflict with, or worse, prohibit innovation. To carry the discussion forward means to be fully aware of the disruptive potential of any innovation, and to shed light on both the challenges and chances of innovation. Precaution also encompasses the responsibility for both pursuing or not pursuing certain actions in order to develop solutions for a particular problem. It demands that, when in doubt, responsible governance should give precedence to the protection of human dignity, human health or the environment, rather than to organizational or economic interests. However, we might perhaps only be able to achieve sustainable development or advance human health by genome modification. It lies within the precautionary principle that precaution and innovation cannot be framed as opposing and mutually exclusive poles.

In order to avoid falling into this trap, a third aspect of a precautionary-based approach is important, namely the need to focus on the particular technology within a specific context by understanding RRI not as rigid, but instead as a step-by-step framework. If there are substantial concerns as well as proven evidence to assume that there are severe risks caused by the use of genome editing, a precautionary-based step-by-step framework would declare it mandatory not to pursue the translation of the respective research into application.

Furthermore, it is essential to emphasize the principles of coherence and subsidiarity within different regulatory regimes. It is crucial for the decision of whether or not specific steps of regulation are required—and if so, on which level—to compare the possible depth of intervention with implemented technologies and their respective framing. Thus, the risks and challenges of using CRISPR for inserting a point mutation could not be assessed just by focussing on this special technique, but within a particular context of application and in comparison to other techniques that are already being used. In other words, a precautionary-based and innovation-driven approach demands to focus on the *relative risks* instead of trying to assess *absolute risks*. Against this background, subsidiarity requires considering regulations on the level of soft law—for example, codes of conduct and recommendations—instead of legal regulations. While it may be necessary to draft national, European or even international laws, it will be at least equally important to develop a sustainable step-by-step framework, and to establish a safety culture for researchers working in both public and privately funded institutions. Again, to successfully implement such a culture without a need for overarching regulation will require efficient regulatory frameworks, public trust in said institutions and an open and transparent discussion on goals, risks and benefits.

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The authors declare that they have no conflict of interest.

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