Opinion on Ethics of Genome Editing

by the European Group on Ethics in Science and New Technologies (EGE)[*]

RECOMMENDATIONS

On the basis of the manifold aspects and potential implications of genome editing in humans, animals and plants, including a particular attention to gene drives, outlined and ethically analysed in the preceding chapters, and noting that the recommendations presented here should not be seen as an endorsement of specific technologies, applications, or application areas,

the EGE recommends to:

1. On overarching matters and concerns

Foster broad and inclusive societal deliberation on genome editing in all fields of application and with a global scope

In its 2016 statement[1] the EGE called for an inclusive societal debate on new genome editing technologies which it deems a pre-condition to permitting the use of these technologies. It recommends that genome editing should not be applied without a general agreement resulting from informed

[*] Opinion No. 32, Brussels, Belgium, 19 March 2021.
Available at: https://ec.europa.eu/info/sites/default/files/research_and_innovation/ege/ege_ethics_of_genome_editing-opinion_publication.pdf
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[1] EGE, *Statement on Gene Editing*, 2016 Available at: https://ec.europa.eu/info/sites/info/files/research_and_innovation/ege/gene_editing_ege_st atement.pdf

global dialogue, constantly striving for global consensus. Public debate should address how genome editing is perceived and assessed by citizens, which opinions, hopes and fears they hold, across fields of application, and whether germline genome editing is seen as necessary and/or acceptable, or would be so under what conditions. Fora for debate should be organised on local and European levels that are integrated in international dialogue, acquiring global scope.

In this context, the EGE proposes an increase of resources to develop and-demploy innovative formats for public engagement (including, but not limited to, education) and deliberation (e.g. citizens' assemblies) on ethical questions related to genome editing. Such deliberation should be based on democratic principles, be open to everyone, involve a wide variety of stakeholders and forms of expertise and be inclusive, interdisciplinary and pluralistic

Avoid narrow conceptualisations to frame debates about the ethics and governance of genome editing

Whereas debates about genome editing often focus on the question of 'how safe is safe enough', the EGE draws attention to the importance of providing nuance to this framing. Resisting this narrow framing, it is necessary to extend the scope of analysis and debate to underlying concepts and approaches, with regard to, notably, humanness, human diversity and biodiversity, naturalness and the value of living beings.

The 'safe enough' narrative limits reflections on ethics and governance to considerations about safety; it purports that it is sufficient for a given level of safety to be reached in order for a technology to be rolled out unhindered, thereby eschewing ethically important questions such as whether genome editing is in fact necessary, acceptable, and under what conditions. Notably, those who are using the technology must ensure that they are monitoring for unpredicted and unintended events, and act upon them accordingly and without delay. This also extends to questions of coordination, inequalities and power relations. In fact, 'safety' or 'trustworthiness' do not pertain solely to technologies but also to institutions and forms of governance in societies – including matters of oversight as well as of democracy and rule of law.

The EGE points to the need to use common conceptual categories with caution and regularly analyse them with regard to their aptness. Traditional dichotomies and divisions, such as those between somatic and germline genome editing, between therapy, prevention and enhancement, or between

basic, translational and clinical research, can offer useful operational distinctions in certain cases, but caution is needed where they constitute artificial, meaningless or misleading boundaries and especially where such categories are imbued with ethical or legal value.

Develop international guidelines and strengthen national, regional and global governance tools

The EGE recommends that the European Commission, together with appropriate international bodies who are also already working in this area (notably WHO, FAO, ISO), develop standards and guidelines for the ethical and safe use of genome editing across all areas of application.

The EGE also recommends to establish regulatory oversight for 'do-it-yourself' (DIY) genome editing tools. The relative ease and simplicity of applying new genome editing tools in humans, animals and plants prompted the development and commercial distribution of DIY genome editing kits, accessible for purchase to anyone. The EGE is of the opinion that their application requires regulatory oversight, which in case of humans may be based on the gene therapy regulatory framework. For the application of genome editing tools in other organisms, the EGE proposes to establish regulatory structures that assesses risk of application for the organism and the environment and certifies their safety. The European Commission is advised to develop mechanisms to avoid or mitigate harm through unregulated availability of DIY kits on the internet, for example, by implementing strong liability rules.

Further recommendations on governance follow in the sections below, applying to genome editing in humans, animals and plants and to gene drives respectively.

2. On genome editing in humans

Engage in global governance initiatives and create a platform for information sharing and inclusive debate on germline genome editing

The EGE asks the European Commission to engage in a global mechanism to guarantee that heritable human genome editing is not prematurely clinically applied and is not applied for purposes other than against serious diseases that cannot be prevented or treated otherwise. On this basis, the EGE calls for the creation of a European Platform to facilitate exchange of

information and a broad and open public debate on the ethical and social implications of germline genome editing in human beings on the basis of sound and evidence-based information. The functioning of the platform should, importantly, also integrate international dialogue and cooperation beyond Europe, for example, with the Global Observatory for Genome Editing, in order to acquire global scope and contribute to processes towards global consensus.

In this debate, awareness should be raised about the implications of widely used terminologies and distinctions, such as those between somatic and germline editing or between prevention, therapy and enhancement, about the need to examine them and to use them with caution regarding their ethical and legal normativity. This responds to the need for values to shape technology and helps to ensure that, in case heritable genome editing will be advanced and applied in countries under certain circumstances, this is preceded by careful consideration of the conceptualisation, acceptability and desirability of the technology.

The proposed platform can also aim at the participatory development of a governance framework that determines, for example, who decides on cases, on what premises decisions are based, and what oversight structures are adequate. Its efforts and actions should be aligned with the work of the WHO Expert Advisory Committee on Developing Global Standards for Governance and Oversight of Human Genome Editing. The EGE recommends that the European Commission collaborates with the WHO and, where appropriate, with the WMA to facilitate the universal adoption of standards on the ethical use of genome editing in human beings.

Establish a public registry for research on germline genome editing

Transparency and evidence-based information is of utmost importance to foster an inclusive societal debate. To support an informed debate, the EGE recommends to establish a European and/or global registry for germline genome editing (that could also be part of the proposed European Platform). It should cooperate with the global registry for human genome editing established by the WHO. The registry should be publicly accessible to ensure transparency for monitoring scientific progress and ethical soundness. Ethical approval and legal compliance must be a precondition for any registry entry.

Project registration is already compulsory for all research on germline genome editing funded by the EU and should become mandatory for all research.

Protect social justice, diversity and equality

Given the potential of genome editing techniques to be used for interventions that are not related to preventing or treating diseases but primarily serve enhancement purposes, their potential for fostering social inequality and undermining diversity should be considered. The EGE recommends to proactively safeguard against enhancement or deenhancement of traits and to ensure that investments in research on germline genome editing have the purpose of protecting health. This also serves protecting human dignity, identity, diversity, equality, social justice and solidarity. In this context, guidelines should be developed that allow research ethics committees to distinguish between technologies and applications of genome editing that are to be considered as preventive, diagnostic or therapeutic, and those that are to be considered as 'human enhancement', if such distinctions are to be used.

Furthermore, somatic genome editing has the potential to alleviate suffering from diseases that could not be treated effectively before. The EGE recommends that access to clinical studies and, once approved, to clinical application in healthcare is granted according to the principle of social justice and without discrimination.

Ensure adequate competencies in expert bodies

Genome editing technologies are evolving quickly and expertise to assess research and application has to keep pace with new developments. It is important to widen the basis of expertise and broaden what counts as relevant knowledge at the level of expert committees, fora and other bodies established to examine and set guidelines and standards for research and application of genome editing technologies. In light of the global variety of views on the essence of human nature, it is important to organise ethics oversight of international research collaboration and prevent ethics dumping.

Such adequacy of expertise is crucial also for ethics committees charged with approving and supervising clinical trials involving genome editing. The EGE suggests that guidelines for safety assessments and risk/benefit determinations of clinical trials are developed and training modules are provided for

research ethics committees and other involved bodies to ensure high-standing and consistent application of ethical standards.

If national legislation of Member States allows research involving human embryos this suggestion also applies to this kind of research. Different Member States have different laws on embryo research. The principle of subsidiarity should continue to be respected.

3. On genome editing in animals

Strengthen oversight of genome editing in animals for scientific experiments according to, and beyond, the 3Rs

The EGE calls for a careful monitoring of the impact of genome editing techniques on the implementation of the 3Rs, including the balance between Replacement, Reduction and Refinement. To this end, (1) the EGE recommends reinforcing reporting requirements with respect to scientific experiments using genome edited animals, including documenting their purposes; (2) the EGE urges research ethics committees and bodies in charge of project evaluation to carefully evaluate the costs/benefits of genome editing experimentation taking the 3Rs framework into account; (3) the EGE recommends that researchers be required to ensure transparency, sharing of data and tissues, and the publication of negative results in order to minimise uncoordinated duplication of experiments.

The EGE also suggests to consider a further R in relation with research funding, Recourse to alternative strategies, as indicated below for nonhuman primates.

Apply strict standards to experimentation with non-human primates and invest in the development of alternatives

Where the advances of genetic engineering techniques provide new opportunities for the development of primate genetic models, the EGE recalls the specific status accorded to non-human primates (NHPs) in the EU legal framework on animal experimentation and supports the view that humans bear strong moral obligations towards NHPs that move beyond the standard 3Rs framework and standard ethics of animal experimentation. It considers that experimentation involving NHPs is morally acceptable only if (1) serious human suffering can be prevented by carrying out scientific research on

primates, that can in no other way be alleviated, and (2) the way of dealing with NHPs in these processes accommodates the wealth of scientific findings on their physical, mental and emotional lives and the modalities of their wellbeing and suffering.

In the context of genome editing experiments on NHPs, the EGE recommends the introduction of an additional 'R' to the 3Rs framework for Recourse to alternative strategies. This principle would go beyond refinement and would require a channelling of research resources into the search for alternatives to experiments and genetic engineering with harmful phenotype expressions. This could for instance take the form of funding bodies requiring researchers conducting experiments on NHPs to allocate part of the research budget to finding alternative methods, for example, through a requirement in EU-funded projects of an integrated work package or clearly defined activities to develop alternative methods

Because of the evolutionary closeness to humans, intentions to study humanisation in NHPs by genome editing are likely. The EGE proposes a humanisation assessment when genome editing is used to modify genes to model human phenotypes in order to anticipate possible outcomes and refinement needs. Such projects ought to be registered in a public database under the responsibility of a public authority. In addition, criteria for constraints ought to be developed (see next recommendation).

Broadly discuss the humanisation of animals and implement appropriate limitations

The EGE calls for further reflection on the implications of, and moral obligations with regard to, genome editing experimentation on animals that results in humanisation, whereby animals may gain functions or characteristics usually attributed only to humans. Given the potential advances brought by genome editing technologies to this domain, in particular in the area of cognition and neuro-functioning, consideration should be given to constraints that should be imposed on such procedures. A scientific and public debate on such constraints and respective criteria would be desirable.

Regulate the banking and farming on animals carrying human organs for transplantation

In the case of developments towards banking and farming on animals carrying human organs for transplantation, the EGE recommends establishing

a strict regulatory framework that fully takes into account safety, security and animal welfare

Prevent unregulated use of genome editing tools

Given the relative ease of use of new genome editing technologies, and in order to prevent an unregulated use outside the regulated professional context, the EGE considers that potential impact on (bio-)diversity by generating new strains should be firmly regulated.

Strengthen ethical oversight of practices involving reductions of animals' natural abilities

Given the possibility to significantly affect natural abilities of animals through genome editing (sometimes designated as 'de-animalisation') and considering that animals with their natural characteristics have an intrinsic value (and not merely an instrumental one), the EGE recommends that, even outside the research context, the purpose of such reduction be explicit, transparent and balanced and subject to ethics oversight in line with the above recommendations.

Ensure the wellbeing of genome edited livestock animals

In a number of instances, genome editing of animals is used to modify or insert traits for commercial purposes. The EGE expects the EU and its Member States to ensure that the health and wellbeing of the concerned animals is assured during all stages of the procedures and of the animals' life.

Reconsider ethically contested industrial farming practices

The debate on genome editing also raises general questions around ethically contested industrial farming practices. The EGE considers wider reflection around sustainable and ethical food production models necessary.

4. On genome editing in plants

Carefully assess the potentials and risks of genome edited plants for agriculture

The EGE recognises that the introduction of new genome edited plants into the agricultural environment may be beneficial in providing products for an increasing population and in facing the impact of climate change. Their introduction could have both positive or negative effects on product availability (notably food), human and animal health, socio-economic conditions, the agricultural environment and the natural environment and care must be taken to minimise harm and maximise benefit.

Develop an (eco)systems approach for evaluating the costs and benefits of genome edited crops

The EGE recommends a systems approach to the evaluation of costs and benefits (including the impact of continuing to use current agricultural practice) in any potential future use of genome edited crops. Such a broadened evaluation could take into account wider impacts on ecosystems and agricultural and natural biodiversity, land use, economic impact and food security. The EGE recommends that regulation should be proportional to the risk – light touch regulation should be used where the modification achieved by genome editing is through techniques such as gene silencing or where the change in the plant could have been achieved naturally or where the editing involves the introduction of genetic material from sexually compatible plants. Where the modification involves genes from non-sexually compatible organisms or where multiple changes in the genetic material have occurred, there should be a detailed evaluation of the changes including a requirement to test the new variety in the field under different conditions.

Develop mechanisms to ensure corporate responsibility

Companies introducing new varieties, regardless of method or provenance should be required to identify the impact of their use on both agricultural and natural biodiversity and the environment.

Investigate mechanisms for traceability and labelling of genome edited crops

It will be difficult to impose a requirement for ensuring traceability and labelling requirements where exporting countries impose no requirements on new varieties or the use of edited varieties as the starting point for newer varieties. The EGE recommends that traceability and labelling should only be required where the modification could not have occurred naturally through mutation or natural recombination with sexually compatible plants. Where multiple genes or those from non-related organisms are inserted, tests could identify such plants, hence traceability and therefore labelling is possible. The Commission should investigate the use of patent registers as a method of identifying genome edited plants. It is recognised that the use of current varieties of plants as the starting material for newer varieties may make such an approach impossible.

Develop measures to support small actors

The EGE acknowledges that any additional risk assessment requirements would prove costly and impose a high regulatory burden which may disproportionately impact small companies and research centres, preventing them from commercialising products or utilising patented traits from other organisations. Consideration could therefore be given to measures to support smaller actors in steering clear of or in engaging with these novel technologies, such as mechanisms to support them in undertaking risk assessments to enter the market

Pay more attention to public debates about genome edited agricultural products

The EGE acknowledges the prevalence of public concern in relation to genetically modified organisms including the lack of public dialogue and informed debate, which accompanied the introduction of GMO products, and calls for more attention to public dialogue on the question of genome edited plants. The EGE cannot endorse a model which assumes that it is the lack of information alone which shapes the public debate.

5. On gene drives

Acknowledge epistemic and other uncertainties

There are many aspects about the systemic effects of gene drives that are not yet known. Ecosystems, as complex systems, have emergent properties that cannot be comprehensively simulated. These unknowns should be acknowledged at the outset of processes of deliberation and regulation, and be openly discussed. Because of these uncertainties, gene drives should not be promoted as a panacea for public health and other problems. Before gene drives are considered as a solution, other measures should have been exhausted. Moreover, gene drives should only be used when the goals and underpinning values have been deliberated and democratically decided upon.

Use gene drives in ways that are based on shared values

The EGE urges all actors to make explicit, and discuss openly, the values underpinning plans to use gene drives, and the purposes for which they are used, proactively trying to include a diverse and broad range of perspectives. Equity and social justice considerations are of particular importance in this context.

Regulate, monitor after release and have mitigation plans in place

The EGE recommends, throughout the process of using organisms modified by gene drives, to monitor their release into the environment on the basis of a mitigation plan for risks and harms. Eco-technologies – such as, but not limited to, gene drives – should also be subject to a consolidated registry and to a coherent regulatory framework of governance as described above.

Retain stock of original organisms

The EGE recommends, because of the uncertainties regarding the traceability and reversibility of gene drives, to retain stock of original, unmodified organisms.