ПРАВОВЕ РЕГУЛЮВАННЯ ВІДНОСИН В ОКРЕМИХ СФЕРАХ ГОСПОДАРЮВАННЯ ТА ГАЛУЗЯХ ЕКОНОМІКИ
LEGAL REGULATION OF RELATIONS IN CERTAIN SPHERES OF BUSINESS AND ECONOMIC SECTORS

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LEGAL AND ETHICAL PRINCIPLES OF GENOME EDITING IN THE EU

Ключові слова: Legal Status of Human Embryos, Animal Experimentation Law, Genome Editing, Ethics, Biotechnological Inventions, European Group on Ethics, Biotechnology, Ethical Considerations, Genetic Modification, Biodiversity, Bioethics.

Biotechnological inventions have considerably advanced over the last decade. The improvement brought to light ethical issues related to these inventions. The ethical issues are broad — therefore, the research is narrowed to the ethics of genome editing in the EU. The ethical views of genome editing are developing alongside the betterment of science. Are human's ethics towards genome editing unchanged? Is there a shift towards genome editing in specific cases? The research focuses on the view of the European Group on Ethics and its possible impact on biotechnological inventions based on genome editing. The first chapter explains the methods of genome editing and cross-cutting aspects of ethics. The second chapter focuses on the ethical issues of genome editing in plants, the third chapter maps the ethics of genome editing in animals, and the fourth chapter deliberates the ethics of genome editing in humans. The conclusion assesses the current ethics of genome editing in the EU derived from the Opinion of the European Group on Ethics. The article addresses legal issues related to genome editing within the EU. It discusses the prohibition of patenting biotechnological inventions based on genome editing, analyzing the impact of ethical aspects on legislation in the fields of patents and biotechnology. Particular attention is given to the legal status of human embryos, laws on animal experimentation, and the regulation of genetic modifications in the context of biodiversity and bioethics.

Introduction. Genome editing is a sensitive topic widely discussed over the world by governments, academics, and people in general. Currently, the discourse on genome editing is revivified due to the new technologies that might be used soon for the public good. Once again, technology accelerates legal and ethical debates on topics which otherwise would stay untouched. The purpose of this article is to analyse the view of the Euro-

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pean Group on Ethics and its possible impact on biotechnological inventions based on genome editing. Generally, the inventions based on genome editing are prohibited from patenting. The prohibition of genome editing related patents is a firm part of majority of European patent laws. Most European states allow patents for biological material (including genes or gene sequences in some circumstances) and prohibits patents for methods of cloning humans, methods for modifying the human germline, use of embryos for industrial or commercial purposes and methods for modifying animal genetic identity which may cause disease unless there is a significant medical utility for humans or animals. An almost identical wording is found in most of the 31 jurisdictions' patent statutes. These 31 jurisdictions are almost all European states [1]. Unless these patent laws change, the probability of biotechnological patent based on genome editing is almost zero. The prohibition of genome editing related patents is largely influenced by ethics surrounding this controversial topic and therefore ethics profoundly influence the legal aspects of patenting. The article discusses the Opinion on Ethics of Genome Editing [2] (further only as "the Opinion") issued by the European Group on Ethics which is an independent advisory body of the President of the European Commission founded in 1991.

Although, someone might argue that there are other legislations important for this research, such as The Convention on Biological Diversity (CBD), authors do not include it in the article because CBD) does not directly address the ethical aspects of genome editing but deals with related issues in the broader context of biodiversity protection, biotechnology, and genetic resources. CBD deals with related issues in the broader context of biodiversity protection, biotechnology, and genetic resources. The article is divided into introduction, four chapters and conclusion. Each chapter clarifies different ethical issues related to genome editing. The first chapter focuses on the terminology, methods of new technologies allowing to edit genome and cross-cutting aspects forming the Opinion. The second chapter embarks on ethical issues of editing plants' genome. The third chapter covers ethics of genome editing in animals and finally, the fourth chapter analyses ethical issues of genome editing in humans. The conclusion sums up ethics for each area.

Terminology and the most influential aspects. *The terminological clarification and methods of genome editing.* The term genome editing "involves the modification of the genome" through targeted adding of, replacing of, or removing one or more DNA base pairs in the genome, regardless of whether the modification occur in a particular or non-coding region of the genome. Genome editing does not necessarily involve transgenesis — the transfer of genetic elements from an unrelated or nonsexually related organism. Various new techniques allowing genome editing have emerged in last years. The techniques used in genome editing are meant to be more precise than those which have in the past been used to genetically modify organisms, and include technologies such as CRISPR/CasX CRISPR stands for "clustered regularly interspaced short palindromic repeats". (where X is usually a digit, e.g. 9), zinc finger nuclease (ZFN) ZFNs are a chain of zinc finger proteins fused to a bacterial nuclease, capable of making site specific double stranded DNA breaks, transcription activator-like-effector based nucleases (TALEN) TAJENs are restriction enzymes that can be engineered to cut specific sequences of DNA.and meganucleases. Meganucleases are homing endonucleases that can be used to replace, eliminate, or modify target sequences of DNA.Genome editing is not to be taken to mean just a change of the whole genome, but also a specific change (or set of changes) in the genome [2, p. 15-16]. The abandonment of the techniques sparked a new discussion on ethics around the world. The European Union's response to the new science development in genome editing is the Opinion.

The cross-cutting aspects of ethics. The formation of ethics for genome editing is an ongoing process impacted by several factors. According to the Opinion, these factors are a language used to communicate genome editing, naturalness, humanness, diversity, "safe enough" framing and governance. The language used to present and explain genome editing to the public is enormously influential towards the public perception of genome editing. Using the language with the religious undertone, such as "that scientists were not only able to "read" the «Book of Life»" (and "see" who we, as humans, are, such as in the context of the Human Genome Project in the 1990s and 2000s) but were now also able to "write" it and "edit" it, have an impact on people's understandings and attitudes. Metaphors are important in guiding the general understanding of scientific advances and are believed to influence people's views on the use of CRISPR/CasX [3].

As also the media play an important role in this, the specific terminology — and the metaphors —

used by media reports also have an impact on people's views and understandings, and not always in the ways intended by scientists. Regarding a technology such as CRJSPR/CasX, it is thus particularly important for ethical reflection to pay careful attention to the words we use to describe the problem at hand. For science, bioethics, and the public, a key question is also: how can our language be honest about the uncertainties in how we will develop and use the technology, and what promise and risk its use holds, without employing terms that trigger gut reaction rather than thoughtful deliberation? [3]. Words may have consequences and they need to be used "responsibly" in order to help ensure that the public and public policy stakeholders are well informed regarding this new technology, since words influence how we act upon and shape the world in which we live [4; 2, p. 15].

Naturalness and unnaturalness play important roles in the perception of genome editing in three dimensions. First dimension recognizes what is natural. "What is natural is often taken to be what is "normal", or even self-evident, or indeed seen as in accordance with the laws of nature — through to natural law and natural rights as a bedrock of human rights". Secondly, the natural is in a close connection (or in a generative tension) with the supernatural, the spiritual, the divine, the demiurgic, "the whole of creation" or "Mother Nature". Thirdly, the natural stands in relation to its antithetic or complementary notions, the cultural, the technical, the artificial, the "human-made". Those three dimensions jointly foreground this key area of reflection: the role of humans — and of humanity — in relation to "Nature", from alienation and emancipation through to belonging and interdependence, from "masters and possessors" through to humility and inspiration, to stewardship and custodianship. Humanness or what means to be a human? The question hunting humans for centuries. Ethics on genome editing gives humanness different meaning: "the human genome, taken as essential or foundational of humanness, becomes up for grabs" [2, p. 17].

Humanness also brings humanisation. What is humanisation? It is "ambiguous and may refer to several different dimensions: it may pertain to a scientific/technical definition (e.g. changing receptor cells on organs of non-human beings into human ones or changing a given sequence of a gene into its human equivalent; thus mice modified to carry one or more human genes are often referred to as "humanised mice") or it may refer to scenarios where cognitive capacity is modified ("enhanced") to such an extent that species categories, or distinctions between human and animal, become blurred (or that new "between-species" categories are created). In the context of the Opinion, a key question and concern is the following: when non-human beings could gain characteristics normally associated with humans, what is their status and what are the rights and obligations that arise? In addition, when considering humanisation, it is also crucial to extend the reflection to its correlates: dehumanisation and de-animalisation (or more broadly de-speciesation)" [2, p. 16-17].

The questions embedded in humanisation need to be asked through ethics of genome editing for all areas — plant, animals and humans. "Diversity" is commonly understood [5] as the richness and variety of distinct objects or types, whether that be at the Ievel of genomes, organisms, species or ecosystems. The Convention on Biological Diversity applies the definition as follows: "the variability among living organisms from all sources including, inter alia, terrestrial, marine, and other aquatic ecosystems and the ecological complexes of which they are a part; this includes diversity within species and of ecosystems" [6]. Measures of diversity take into account not only the variety but also the commonness or rarity of a species, trait or object [2, p. 17]. Why is diversity important within ethics on genome editing? The answers lie in how diversity serves the interests of humankind. In the ecological sphere, evidence indicates that more diverse ecological communities are more stable and resilient than those that are less diverse [7]. A wider range of genes or species within an ecosystem improves its functioning and adaptability. Humans benefit insofar as they are dependent on, and profit from, a flourishing natural world. For others, diversity derives its value from the presumption of an inherent or intrinsic value within all beings, that nature is worthy of moral consideration, and that this confers relevant obligations and duties [8].

Debates surrounding such propositions invoke notions of human responsibility towards non-human species, human custodianship over nature, as well as critiques of human hubris in our relationship with nonhuman life (commodification of nature, "who are we to decide?" questions). An examination of humans' responsibility towards other species must also consider human responsibility towards other humans. This is particularly relevant

in light of the potential of genome editing to impact on the scope and nature of human genetic variation [2, p. 18-20].

Safe enough framing is all about safety and risks of genome editing. According to the Opinion, there are three perspectives of this framing. Firstly, the "safe enough" narrative correlates with the risk analysis framework and more particularly with the fraught notions of "zero risk" and of "acceptable risk". The latter is problematic in several ways. We always take risks. Which risks we accept depends on the situation and the possible benefits. In this context, the "safe enough" narrative can lead us to falsely believe that if a technology is "safe enough" there are no risks. Further, what is considered "safe enough" is highly context dependent. What is needed instead is a consideration of the complete decision problem; to take sound, well-reasoned decisions; to look at both the pros and the cons; indeed, to consider not just the risks and costs but also the possible benefits, in the widest sense, and the distribution thereof [2, p. 20].

Secondly, there is also a fear that focusing solely on safe enough narrative becomes the alpha and omega, both the cop-out and the carte blanche as well as the tree that hides the forest. Thirdly, the "safe enough" framing is reminiscent of the "technological imperative", the notion that "if it is technologically feasible then it ought to be done". This eschews more ethically pressing questions such as whether genome editing is in fact necessary, acceptable, and under what conditions [2, p. 21].

The safety of genome editing must be guaranteed by somebody, in this instance, it is a government. 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 [2, p. 21].

Governance is a crucial and complicated aspect of genome editing. A first component is the state of the existing and emerging legislative and regulatory approaches across the different purposes and domains (humans, non-human animals, plants, microorganisms, gene drives). The most salient feature of the current situation is the lack of robust structures of global governance, as strikingly brought to light by the genome editing revelations at the end of 2018 [9; 2, p. 21]. There is an eminent need for a global governance system. Key questions with regard to the different aspects of governance are: How are decisions to be made? Who decides and who ought to decide? These questions pertain to the geopolitical level (e.g. the strong influence of the USA and China in the global governance arena to date), to the disciplinary level (e.g. divisions and dominance of certain branches of science; primacy of some natural scientific disciplines over other fields also in the humanities and social sciences), to the stakeholder level (the need for participatory approaches, questions of public trust), extending to the wider public (going beyond "present generations" and "political participation") and anticipatory governance. With respect to the collective experiments in developing forms of governance of genome editing, across the globe, we should address how we can establish systems which can both monitor developments and enable to draw lessons (including mutual learning across different areas in the ethics and governance of sciences and technologies, such as "artificial intelligence", GMOs, genome editing) [2, p. 22]. These aspects combined create a unique start for an incredibly challenging task — formulating ethics on genome editing. All above mentioned questions must be asked and answered.

Genome editing in plants. *Modification of plants.* Plants are a beautiful and useful part of nature. Plants provide us food, energy, home, joy, shade, water. The progress of science also means the progress of plant's research. Science provides almost unlimited power to modify our environment. The problem is no longer as to what can be done, but rather what should be done. The economic impact of choosing to use or not use plants produced using any new technologies is likely to be significant and should be addressed by public authorities and society at large [2, p. 58]. The betterment of plants has been helping humankind for centuries. The first farmers would choose the seeds of plants that produced the most favourable traits, such as that with the most fruit, to plant in the following season. Scientists use different methods. Deliberately induced mutations using chemicals or radiation or genetic modification by changes at random points within the genome of plants have been used for a long time to attempt to produce new ("improved") varieties of plants [2, p. 58-60].

New plant varieties. Most commercially produced plants currently cultivated are the results of deliberate modification and subsequent selection. This process can (and does) take considerable time. New varieties are continuously being created that are better suited than current varieties to the local condi-

tions or have desired agronomic or other desired characteristics — to meet challenges including responding to anticipated consumer choice, longer shelf life of the products or to defeat weeds and pests. To meet "plant variety rights" rules for registration as a new variety, the modified plants must be (i) new, (i.i) distinct (where they are clearly distinguishable from other known varieties), (iii) uniform and (iv) stable (characteristics are unchanged after repeated propagation). The effective lifetime of a new variety depends on the "crop" but is relatively short, sometimes no more than five years. Many of the plants obtained using new genetic technologies may not be suitable for particular agricultural conditions and will be crossed with appropriate varieties to further improve that which is actually used in production. "Traditional techniques" (including mutagenesis) for producing new plant varieties have received little press and almost universal acceptance within Europe. On the contrary, most EU Member States have resisted using varieties produced using "modern biotechnology" [2, p. 58-60].

Although, there is a little evidence of serious or irreversible damage to the widespread use of crops using genetically modified organisms in the rest of the world [2, p. 61], there is the precautionary approach applied by Members of EU (further only as "Members") that blocks the use of plant products containing the derivatives of GMOs — genetically modified organisms (further only as "GMOs"). When Members are so afraid to fully embrace these plant products, why do we want genome editing in plants? New varieties of plants are introduced into the market for many reasons, including improvements in characteristics — yield, resistance to pests, adaption to particular or changing environments and even catering to the whims of consumers. Many changes can be accomplished by traditional farming methods that require crossing with related sexually compatible varieties, but this is a slow process, requiring many generations.

Understanding the impact of climate change, including desertification, drought, or even excess water in particular climatic areas, provides an impetus for producing new varieties of plants that can be adapted to the changes. Genome editing provides greater precision than genetic modifications used for last 30 years as to the site of changes and makes it possible to (largely) accurately identify the position of modification in the genome, resulting in greater precision in producing new varieties, and hence more rapid introduction of new, "improved" varieties to the marketplace. New genetic technologies provide systems for identifying the targets for disease-causing pests in plants and in many instances the defence mechanisms developed by plants to attempt to mitigate disease. Genome editing could then be used to make the plants hardier and less susceptible to the many challenges which nature provides. Genome editing using CRISPR/CasX (Cas9, Cas12 or similar) has revolutionised the tedious process by allowing acceleration of the initial selection process — already the process used in plants is a cheaper and much faster method for achieving the same ends. The system permits gene knock-out, deletion, insertions and even gene silencing [2, p. 65-67].

How do we regulate the new genome editing technologies in plants? In the European Union (further only as — the EU), the plants products containing GMOs are regulated by Directive 2001/18/EC of the European Parliament and of the Council of 12 March 2001 on the deliberate release into the environment of genetically modified organisms and repealing Council Directive 90/220/EEC (further only as — the GMO Directive). This directive is also applicable to the new genome editing technologies in plants. The definition of GMO according to art. 2(2) Directive 2001/18/EC of the European Parliament and of the Council of 12 March 2001 on the deliberate release into the environment of genetically modified organisms and repealing Council Directive 90/220/EE is "genetically modified organism (GMO) means 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".

Safety of genome editing in plants. All agricultural products contain mechanisms developed by the plants as protection against predators. Some use spines or thorns, and many use various types of poison [2, p. 69]. Almost all plants contain some toxins which in certain amounts can be harmful to human health. It is unlikely that a modification will have deliberately or incidentally introduced new toxins into a plant, but the introduction of new genetic material will almost certainly result in a change in the production of some chemicals by a plant — hence some form of risk assessment would normally be expected. Tests to ensure that toxicity remains within safe bounds would always be necessary for any new variety, regardless of the technology used in its production. What therefore constitutes safe? Is a new variety to be tested on the basis of "as safe as

that currently on the market"? Does the new variety have to be safer than that currently used? Should the whole system, including chemicals used, land used and protection (or otherwise) of the agricultural diversity be taken into account in deciding on safety? Should the requirement "based on an examination of the potential benefits and costs of action or lack of action (including, where appropriate and feasible, an economic cost/benefit analysis)" be part of this analysis of safety? [2, p. 70-71].

Safety as a part of ethics on genome editing in plants is hugely influenced by potential health risks not only for humans, for animals as well. Most of new varieties are meant to be used as food for livestock animals. Safety of new varieties containing GMOs might be the hardest obstacle towards the public acceptance of genome editing in plants.

Identification of plants with GMOs. In EU, there is a requirement of traceability of plants products containing GMOs due its yet unclear effect on humas. How can we achieve a well-functioning system in which it would be possible to identify these products? The answer is unsatisfactory. Traceability requirements apply in the EU, where the producers of the plant or seed have to provide documentary evidence to show that a product contains, consists or is produced from a GM0 [35]. The cost could be considerable and non-European producers have to, but may not be willing to comply. How can the perceived concerns of the European consumer be addressed? How do traceability criteria work given that the products are grown throughout the world, and if not regulated in one jurisdiction, may be used as the starting material for a host of new varieties? [2, p. 73]. The traceability system might work well in the EU with the EU based producers and maybe with producers outside of EU who would like to conduct business in the EU. The rest of the world might not co-operate at all.

Biodiversity. The impact of genome edited plants on the natural environment could be both positive and negative. If a gene inserted into a plant is transferred to natural relatives the result could be the creation of weeds and the loss of control (e.g. herbicide tolerance). The opposite may be true if the new genetic element has food or feed advantages or is toxic to some insects — allowing the plants within the environment to better adapt to their environment. The effects may seriously impact the ecosystem — resulting in a deleterious change in the whole environment. Increase in yield per hectare, on the other hand, may allow the retention of uncultivated land which could impact the natural environment in a positive manner. An example is deforestation in order to grow crops which is a major issue in tropical regions where the needs of the European consumer may impact on the lives and environment in unexpected ways. Should companies introducing new varieties, regardless of method of the provenance, be required to identify the impact of their use on biodiversity and the environment? [2, p. 74]. Biodiversity of many agricultural areas is practically non-existent. The ethical question in the centre of biodiversity is whether the humankind will use new varieties to preserve biodiversity where necessary or will use it to worsen situation.

Industrialisation of agriculture. The impact of the industrialisation of agriculture should not be taken lightly. New varieties have often resulted in greater industrialisation as the selected traits impact on the way the crops are grown. This could be exacerbated by the ready availability of new traits specifically chosen to (apparently) benefit the farmer [2, p. 75]. There are three concerns. First, larger farms have an impact on the general biodiversity (rather than agricultural biodiversity) through the disappearance of hedges and nonfarmed areas of a field. Second, smallholders struggle to compete with larger farms, even where the quality of their produce may be higher, or more desirable to consumers. Thirdly, the number of individuals employed in agriculture falls as industrialisation occurs [2, p. 75]. The industrialisation of the Earth is an ongoing process where genome editing in plants play an influential role. The extent of this role is yet to be determined.

Biosecurity. There is a concern that modern techniques of genome editing may impact adversely on biosecurity when defined in this manner. In particular, the security of supply of particular major crop species could be impacted, especially where possible monocultures are used. Food security has become an important issue, particularly with a growing urban population, the impact of climate change, limited land available for agricultural expansion and the need to have an efficient distribution system where losses during transportation are minimised. The new techniques may have a role to play [10]. What incentives could be introduced to ensure that new varieties address biosecurity and security of supply for food, feed, fibre and fuel? [2, p. 77]. These incentives should be debated by governments, private companies and public, otherwise the world might end up with uneven distribution of new varieties.

Justice of using plant products with GMOs. Modern techniques for the production of new varieties, whether or not by genome editing, have been the prerogative of large seed companies, due to the cost of producing them. This has led to the monopolisation of the production of seed within a small group of companies, and considerable public reaction to some of these companies. Very considerable testing of new varieties produced using genetic modification ensuring their safety resulted in high costs, which made the production of such varieties by small companies or research organisations prohibitive. This in turn led to the monopolisation about which there are many concerns. The techniques could have an impact on distribution systems, resulting in quality food becoming available where it is needed, in the urban environment. Should the requirements linked to the introduction of plants developed with the techniques of mutagenesis involving genome editing be the same as that for other GMOs, the ability of small companies, research organisations or universities to produce new varieties (initially for local use) would be seriously curtailed, and this could result in monopolisation due to the costs entailed in assuring safety. Any additional risk assessment requirements could prove costly and impose a high regulatory burden, further preventing smaller companies and research centres from commercialising products. Should consideration be given to structures that support smaller actors to undertake risk assessments and enter the market? [2, p. 77]. The higher cost of production of plants with GMOs, especially for small actors, is a considerable turn-down. How this ethical concern will be addressed in the EU will impact the overall perception of plants with GMOs.

Societal considerations. There are various societal views and issues that impacts ethics. One of them is a food quality. Many reject the importation of cheaper foods and choose to buy regional varieties. There are many who argue that there is no need for new varieties or products within the food sector. The debate about scientific risk could once again become an overly debate about food quality, paysan survival, and trade policy [2, p. 78]. Also, some views were formed without having all information on genome editing of plants. There is a clear need for honest dialogue and the inclusion of all the public in framing the decision-making process for introducing new products to the market. There is much false information or hype provided by all sides in the debate about new technologies that produce this most basic commodity [2, p. 78]. Price of new varieties' food is a concern as well. The effects of increased prices and availability where strong regulation is required should also be considered. This would impact on the poorest segment of society [2, p. 78]. Lastly, there is a concern that patents may inhibit the use of new varieties by farmers due the cost of patenting and exiting patents.

Genome editing in animals. The ethics of genome editing of animals can be considered from two perspectives, or on two levels: the one of an instrumental use of genome edited animals for purposes of human benefit, from human health to food; and the welfare of animals with respect to their intrinsic value. The EGE is, however, also aware of the problematic nature of this distinction, with any discussion about animal welfare positioning, humans as guardians, with power over them. In other words, even taking this perspective can be problematic as we cannot escape our human viewpoint. EGE calls attention to:

- our relationship with non-human animals and, as part: of this, our practices to "design animals" to fit the environment as we are "engineering" it, opposed to an understanding of the environment shaping (us) animals over time, involving sustainable practices of mutual adaptation and care;
- animal rights, animal ethics, and a wider related literature, attempt — or warn against — fitting animals into our general ethical frameworks, a situation that might be further enriched in view of our evolving, scientific understanding of animal cognition and emotions, and in view of the human publics' evolving sensitivities;
- the various levels of concern at play: those that pertain to human welfare, to species, or to ecosystems in their entirety.

On this basis, the EGE identified a series of key questions with regard to genome editing in animals. Does genome editing affect the implementation of the 3Rs and the balance among the three principles? Does it, for example, contribute to refinement, at the expense of reduction? What are the implications of and which should be the limits to "humanisation" of animals? Are there specific requirements for the use of genome editing in non-human primates, beyond those already established? In what way is animal welfare in farming fostered or hampered by genome editing and what criteria should control its application? Can genome editing increase both animal welfare and efficiency in farming? What are the broader implications of genome edi-

ting for biodiversity? [2, p. 48]. The bulk of unanswered questions forms ethics on genome editing in animals, it aims to the fundamental ethical concern: Are we protectors or users of animals?

Genome editing and the 3Rs. Replacement. On the one hand, genome editing helps to overcome technical and financial obstacles to animal research [11]. On the other hand, it is possible that genome editing will offer opportunities to replace animal experimentation with laboratory methods that do not require the use of living animals [12]. Genome editing techniques can, for example, be used to replace standard laboratory-grown animal model organisms by generating cell lines with specific characteristics that provide disease models. Another possibility to replace animals in research is the creation of organoid models using new genome editing techniques. Although unable to substitute the use of animals, organoids provide an additional screening step between cell-lines and animal models meaning fewer potential therapies and interventions will move on to testing in animal models and a higher rate of success in those animals. Scientists even expressed concerns about further developments in organoid and synthetic tissue technology potentially placing a greater onus on scientists to carefully justify their requirement for animal experimentation [13].

Of course, the development and functioning of organs within a greater whole, a physiological system, cannot be replicated without using whole animals. But in this context, genome editing has made almost any organism amenable to genetic manipulation and may result in mammals being more readily replaced by simpler organisms, if scientifically appropriate [12; 2, p. 48-49]. The replacement of living animals has been a controversial aim over last decades. As technology progressed, humankind progressed morally and ethically. Nowadays, certain portion of public wish for abandonment of traditional animal experiments and testing. If the decrease of animal experiments would be communicated to public in the right way, ethics on genome editing in animals might shift towards the acceptance of it.

Reduction. It has been stated that the impact of genome editing might be "most apparent in our attempts to reduce the use of animals in experimentation" [12]. Reduction can be defined as obtaining the same amount of data with less animals or obtaining more data with the same amount of animals. It implies the use of methods that minimise the number of animals used per experiment, which includes appropriately designed and analysed animal experiments that are robust and reproducible, and truly add to the knowledge base [14].

However, there appears to be potential for both reduction and increase through genome editing. CRISPR/CasX means that, for example, fewer mice are likely to be required to establish a given line. However, the relative efficacy and ease of use of CRISPR/CasX mean that more researchers are likely to use it to research questions in whole animals in ways that were previously, technically beyond their reach. This might increase the overall number of animal experiments performed, which might in turn mean decreased animal use relative to the rate of knowledge production, but also an increased rate of experimentation and increased risk of poorly planned or coordinated research [11; 2, p. 50]. The replacement and reduction go hands in hands, the right presentation to public might bring a shift in ethics on genome editing in animals, the shift of ethics that might allow genome editing in animals at least for research purposes.

Refinement. Refinement relates to minimising animal suffering through the advancement of studies on research animal welfare by exploiting the latest in vivo technologies and by improving understanding of the impact of welfare on scientific outcomes [14]. "In vivo" refers to experimentation done a whole organism, rather than in live isolated cells. A contribution to refinement by genome editing is not obvious. Animal geneticists still need to generate embryos for microinjection of guide RNA/CasX/template cocktails, and these zygotes still need to be delivered to pseudopregnant females. There is a drive to refine such procedures, for example, by developing robust non-surgical embryo transfer techniques. But these refinements are not specifically affected by genome editing methodologies [12].

There are risks to the welfare of experimental animals also due to technical difficulties in the use of genome editing. Off-target mutations may lead to loss of function of a gene, adverse events, or even fatal abnormalities [15]. They may consequently cause the animals further pain and suffering, due to the off-target effects, and death as they succumb to adverse off-target effects or are killed. On the other hand, genome editing could be used to decrease the suffering of research animals, for example, by decreasing the occurrence of unwanted genetic effects. Moreover, it was argued that routine

genome editing of non-human primates could come within reach, substantially compromising their welfare and quality of life [16].

It has to be added here that all involved appear to agree that, in general, far too little data exist to reach any robust conclusions about off-target effects associated with CRlSPR. Indeed, increased scientific refinement here-the provision of much better models of disease-associated human genetic variation-can be viewed as an ethical good in itself, since it will arguably result in more rapid and significant advances in scientific understanding i.e., progress towards better treatments. It is in this sense that research itself can be viewed as an ethical good [12]. However, genome editing could lead humans to ignore the predicament of the animal and to accept negative effects on animal welfare for the sake of other goals, although this risk could be prevented by using less drastic gene drive designs and using them to promote animal welfare [17].

Thus, we find that with genome editing a possible new balance between the 3Rs, as compared to what is usually the case, might appear. Genome editing can contribute significantly to refinement, but apparently not to reduction overall. Although the 3Rs are considered equally important, how we balance them does sometimes change with different technologies [2, p. 50-52]. How to balance of 3Rs seems to the key ethic issues of genome editing in animals. Current ethic in this area suggests that under certain conditions and for specific aims, genome editing might be ethically acceptable.

Humanisation. The idea of the "humanisation" of non-human animals is ambiguous and has several dimensions: it may imply a scientific/technical rapprochement of animals to humans, for example, changing animals' receptor cells on organs to human ones in order to impact immune response, or knocking out specific genes, or changing a specific gene sequence according to the human equivalent. Mice carrying a human gene are, for example, often referred to as "humanised mice". Humanisation might also refer to scenarios of enhancing animals' cognitive capacity to such an extent that the species categories or the distinction between human and animal become blurred (or new "inter-species" categories are created). The potential to change the nature of animals, sometimes referred to as "de-animalisation", i.e. to add or remove certain capacities from animals (such as cognitive capacities or the ability to feel pain), is of ethical concern. In that regard, humanisation can also be understood as a form of de-animalisation. A main concern identified with respect to non-human primates (aside from broader ethical questions around the use of primates — and other animals) is the potential of genome editing research to humanise them. With regard to xenotransplantation research and its clinical application, the outlook of large-scale farms of pigs carrying human organs raises major concerns [2, p. 52-53].

Humanisation or de-animalisation are ethically challenging concepts. The question here seems to be whether humankind really need for greater good edit genome of animals in this fashion. When we compare possibility of having animals with human features to the need of pigs carrying human organs, we see the difference. The difference is in the ethics of it. While the necessity of animals carrying human organs might be ethically justifiable, the existence of animals with human features might not be.

Genome editing in animals and biodiversity. Theoretically, genome editing could be used to reintroduce extinct animal species or restore populations of endangered animal species. Using genome editing for these purposes is a niche application that is still in an exploratory research phase and should be considered with caution and with careful analyses of potential consequences before being considered in practice [18; 2, p. 57]. The restoring of extinct animals seems a noble cause, it is one of the positive effects that genome editing might have.

Genome editing in humans. The Opinion focuses on what it considers to be two key aspects of particular importance regarding somatic and germline genome editing [19] in humans. First, there are fundamental conceptual considerations that are crucial for an ethical assessment of genome editing: applications, also with regard to their global impact. They concern views on the nature of human beings, the relevance and status of the genome in this, the identification of humans as a species and the implications of belonging to it, as well as the relationships of people to themselves, to each other and to the environment. Second, the safety of a technology is generally seen as a criterion of crucial ethical importance. A technological intervention is meant to benefit people and society without undue (disproportionate) negative consequences for individuals or groups.

There are different views on what constitutes a benefit, a risk or a harm, depending, among, other factors, on scientific evidence, but also on personal preferences and values, as well as wider contexts of

culture, societal attitudes, existing governance frameworks and the framing of the scientific landscape. Determining what is "safe enough" is not only about knowledge, but also about values, and scientific theories and practices are themselves value-laden. There is a longstanding practice of weighing potential benefits and risks in clinical research and in healthcare for somatic genome editing, but with regard to germline editing the question of safety is more complex. Its difficulty mainly relates to the fact that the genetic conditions — the biological starting point for the entire organism throughout the whole life of the person — are changed, and that future generations will be affected by this. The question as to which criteria must be fulfilled so that germline genome editing can be considered "safe enough" and how to come to this conclusion requires discussion [2, p. 23-24]. Ethics of genome editing in humans are the most challenging thanks to the fact that it is about humankind and there is a justified fear that how we shape ethics might reflect hundred years later.

Humanness and naturalness. The question of humanness and thus of what constitutes a human being can be discussed from various perspectives, including biomedical, philosophical, sociological, ethical, or religious ones, and by referring to biological, ontological, or social features. It is an anthropological question that people have dealt with for centuries. What is typical for the human species, what is unique to the human species? With the technical possibility of bringing together eggs and sperm outside of the female body, the emergence of a human being came into the hands of third parties who are otherwise not involved in the process of natural conception. It thus became available for intervention. With the CRISPR/CasX techniques, the opportunity for intervention has become so specific that even the genetic make-up of the human embryo is at the designer's disposal. Is this an intervention in humanness? Biologically speaking, no — not as long as only such genetic changes are made that lead to genes that are otherwise present in humans. Even if DNA from another organism is introduced in a human genome this does not change the humanness of that entity.

However, the question arises whether a change in the initial genetic condition of a human being fundamentally alters the nature of humanness or rather the relationship between humans by making them unequal with regard to their genetic starting conditions: those from one human being can be submitted to deliberate and targeted editing by another human being. In this manner, an engineering/design approach in human genomics may undermine fundamental equality of all human beings, which implies that there are no discontinuities in the range of humanity that would accord some humans a lower status than others [20].

Such equality implies that all human beings have equal worth and are accorded human dignity, without exception. This basic equal regard cannot be earned and is never a matter of merit, desert or design. How can it then be classified, ethically, that a human being does not owe his or her genetic make-up to chance — so to say to "nature", in terms of independency from deliberate and targeted human intervention — but to the deliberate shaping of it by other human beings? Is this intervention so fundamental that no human being should ever assume responsibility for it, and that germline genome editing should hence be categorically forbidden? Or does the possibility of the intervention make it necessary to assume this responsibility, for example when it enables to prevent a serious disease? That the intervention in the genome of a human embryo is considered particularly serious is partly due to the consequence of this intervention — the change is also passed on to next generations. It is also due to the perception that the genome is something very special for living beings, as discussed under the notion of "genetic exceptionalism".

A view on the human genome as being the "code" of the individual is countered by the fact that genes do not (solely) determine the individual, their personality and life; they only provide a framework within which human beings can determine themselves and lead their lives in many different ways. The role of the genome for the individual and the human community is also assessed differently in different cultures and can change over time. A related question arises as to whether a human embryo whose genome has been edited is still the same human being after the occurred alteration. Is the genome of a human being considered so essential for the dignity and identity of a person that a genetic modification at zygote state makes her a different person? Or is it rather her entire living as a being with body, mind and emotions, her narrative? This question refers to the concept of genetic exceptionalism as well, in the sense that the genetic component of a person's individuality is considered more important, or in another way different from other, non-genetic factors that make a person.

Genetic exceptionalism and determinism would imply that editing a disease-causing gene in a zygote means creating another human being or an intervention "by" creating another human being, rather than treatment or prevention. It is clear that there, is no one scientific, unambiguous and thus binding answer — as to what the relation between the genome of a human embryo and humanness and naturalness is, and what ethical orientation this can provide. Rather, the need arises for a broad, inclusive and nuanced social debate on the foundations of our view (or indeed many possible views) of humanity, which takes all perspectives into account and brings them into discussion [2, p. 25-28]. Are we all humans even with edited genome? Are we all equals even with edited genome? The ethical dilemma is palpable, the EGE asks lots of questions, but answers are not given.

Diversity. Genome editing, with its ability to modify genome types, bears on diversity in important ways. New genome editing techniques open the possibility to expand or narrow genetic diversity across the different domains of their application. Regarding humans, diversity is commonly understood as the richness and variety of cultures, age, gender, beliefs, and world views, amongst others. It also entails biological features such as genes.

Measures of diversity take into account not only the variety but also the commonness or rarity of a trait or feature. In many contexts, diversity has risen to the status of an accepted "good", and a social goal to be protected and promoted. The Convention on Biological Diversity, for instance, emerged out of a universal consensus that biodiversity is of immense value to humankind and must be protected by international law. Similarly, by the early 2000s, the protection of cultural and/or linguistic diversity had emerged as a socio-political movement with the endorsement of international bodies such as UNESCO. In order to significantly influence the diversity of the human gene pool, a very broad use of genome editing on embryos over many generations would be necessary.

Currently, such a development is not foreseeable, but no definite statements can be made about future application scenarios. That genome editing presents the prospect of curbing serious diseases and disabilities prompts important discussions about both the biological impacts of "tinkering" with the reservoir of human genetic variation, as well as the social implications. This is thus about the particularly fraught issue of determining the kind of people a society might want to have, and who gets to decide that a specific variation is — or is not — a problem in need of a genetic, technological "solution" [2, p. 27-28]. To preserve the diversity of humans is the key issue here, a power or capability to determine what is diverse and how to protect diversity is unknow for now.

The distinction between therapy, prevention, and enhancement. Although therapy, prevention and enhancement cannot always be dearly separated from each other, there are some definitional characteristics that provide orientation. Prevention and therapy relate to a disease or impairment, whereas enhancement refers to the improvement of a statistically and medically "normal" feature or function. Prevention means the avoidance of a disease or impairment, respectively avoiding their aggravation or recurrence, whereas therapy aims at restoring health or alleviating symptoms of a disease. The use of genome editing for purposes of therapy (also depending on the seriousness of a disease) seems to be far more acceptable for most people than its use for purposes of enhancement.

Therapy can only apply if there is disease and thus only refer to individuals who are suffering from a disease. A human embryo in an early developmental stage can be a carrier of a gene that will lead to a disease in the course of further development but cannot suffer from a disease in the way a born human being can, with physical symptoms and the personal and social experience of illness. Therapeutic genome editing can therefore only apply to somatic genome editing. Enhancement can be applied with regard to different kinds of features and impact, for example, biological, cognitive, or social functions. It aims at changing them in a way that is considered as making them "better than normal" for the individual concerned or better than what is "normal" for humans in general. However, what is "normal" is often not clearly defined and its definition changes over time and among societies. Normal can, for instance, refer to a statistical distribution, to a defined threshold or to a biological function of an organ. To name an example, a new medical definition for the thresholds delimiting high or low blood pressure can render thousands of people ill who were previously considered healthy, without anything having changed in their body [21].

Dis-enhancement is discussed less often. When it is, it usually refers to a removal or worsening of biological functions. Some persons who are born deaf, for instance, do not perceive their deafness as

a disease or impairment but rather as a condition that is normal for them and that contributes to their specific culture with, for example, their own language. They may therefore also wish their children to be deaf and, after preimplantation diagnosis, transfer only the respective embryos. With germline genome editing, it would be technically feasible to alter a gene so that deafness occurs. While the community concerned may not describe such intervention as dis-enhancement, the wider public may perceive it as a diminishment of capacities usually present in humans.

Prevention has been defined as activities that are designed to reduce the likelihood that something harmful will occur, or to minimise that harm if it does occur. There is a blurring line between prevention and enhancement; some genome editing modifications could serve both objectives. The EGE holds that distinctions between therapy, prevention and enhancement can be of some use for assessing the ethical acceptability or even desirability of somatic and germline genome editing. They can be helpful for weighing potential benefits and harms, mostly with regard to the alleviation or avoidance of harm justifying greater risks than the enhancement of otherwise "normal" functions [2, p. 28-30]. It follows that how public understand the distinction among prevention, therapy and enhancement may significantly shape ethics on genome editing in humans.

The safe enough criterion. Safety often is at the centre of the debate on genome editing. All too often, the (more or less explicit) underlying assumption is that it is enough for a given level of safety to be reached in order for a technology to be rolled out; and all too often, ethics and governance reflections get restricted to safety aspects. The EGE however argues that a technological intervention has to be "safe enough" in the terms of a broad and nuanced understanding of the notion. Against the background of a bio-psychosocial understanding of health, much has to be considered. Are there medical risks for the application of germline genome editing against serious diseases or impairments? Are there psychological risks for individuals after germline genome editing regarding their self-perception and their social relationships? Are there social risks with regard to discrimination towards people with disabilities or inherited disorders, as is already discussed regarding prenatal or preimplantation diagnostics? Are there long-term risks of heritable genome editing for the concerned individual or for future generations that can hardly be foreseen?

Safety cannot merely refer to the absence of any risk, as no technological intervention is without risk. The question rather refers to what can be considered as "safe enough". The very first prerequisite for an intervention to be considered safe enough is knowledge about its effectiveness in terms of potential benefits, and about potential harms. There must be scientific evidence that the technological intervention contributes to the solution of the problem for which it is designed; and the robustness of this evidence needs to be assessed. The second prerequisite refers to the ratio between risks and potential benefits: risks must not exceed benefits [2, p. 31-32]. The criterion of safety in ethics is paramount. Regarding genome editing in humans the determination of safety if rather a balance exercise where we need to balance positive outcomes against ethical concerns.

Safe enough in the context of somatic genome editing. There is no novelty in the definition of "safe enough" in genome editing of somatic cells. It follows the same ethical conditions recognised by the scientific community regarding research and the clinical application of interventions for therapeutic purposes, mainly the evaluation of risk/benefit proportionality by the researcher, the ethics committee, and the physician together with the patient, respectively. Furthermore, the informed consent of the study participant or the patient is necessary. The EGE wants to stress the importance of specific genome editing expertise within ethics committees charged with approving and supervising such activities as clinical trials or the use of therapies involving genome editing. These committees have the difficult task of determining, on a case-by-case basis, when genome editing is warranted. It goes without saying that, in general, ethics committees have highly competent members, but not all of them are familiar with the technical aspects of genome editing. Therefore, it could be considered whether specialist bodies should make risk/benefit determinations on a project/case-specific basis, rather than leaving those determinations to research ethics committees, which are generalist and may not have the expertise to make these assessments. For medicines, the Clinical Trial Regulation lays down, that Member States shall ensure that the assessment is done jointly by a reasonable number of persons who collectively have the necessary qualifications and experience [22].

However, there is room for different organisational approaches to fulfil this requirement [2, p. 31-32].

A specialised body for assessing the risk on case by case basis in the EU may seem as viable solution and it would also guarantee that experts would issue decisions. We may go even further, we may establish a specialised body in the EU that would licence research bodies in all EU Members. These research bodies would be accredited for conducting research in genome editing in humans. Why do we need such bodies? The lack of research in genome editing in all areas is notable and distort the debate about genome editing.

Safe enough in the context of DIY genome editing. A benefit/risk-analysis is more difficult the more institutional frameworks of clinical research and healthcare are left behind so that existing governance frameworks do not apply. This is true for so called "do-it-yourself kits" (DIY kits) for genome editing that have been commercially offered by promoters of the so-called "bio-hacking" movement. The movement presents itself as advocating for a "democratisation" and acceleration of science by enabling "anyone" to experiment with latest biological techniques [23].

After first "at home" use cases of DIY CRISPR engineering were reported, regulatory institutions have reacted to the risks of private experimentation with genome editing tools. Existing EU legislation has been referred to [24], and in several EU Member States genome editing is only allowed in licensed laboratories, implying that IDIY applications are prohibited. The German federal genome editing law, for example, provides that genome editing can only be conducted in laboratories for genome editing (free translation of the authors), ("Gentechnische Arbeiten durfen nur in gentechnischen Anlagen durchgefuhrt werden, Gesetz zur Regelung der Gentechnik"). In 2017, the European Centre for Disease Prevention and Control (ECDC) recommended that national authorities review their authorisation of commercial DIY kits. Progress in this area may lead to intentional attack or accidental contamination with modified viruses or bacteria [25].

Beyond security concerns of this kind, DIY genome editing kits raise ethical questions around, for instance, naturalness, biodiversity, humanness, safety and responsibility. A better understanding of the current situation, through studies of more recent developments around DIY genome editing activities and existing and possible governance tools, would be an important step towards establishing how a clear and coherent European regulatory approach to it should be developed. It is without doubt that regulation is necessary as an unregulated use of DIY genome editing, tools can clearly be hazardous [2, p. 33-34]. Leaving genome editing in humas for DIY scenarios is harmful and unwanted. The legal prohibition of such activities in all EU Members is desirable.

Safe enough in the context of heritable genome editing. The proportionality of benefit in terms of preventing a serious genetically transmitted disorder has to be balanced with the risk not only of not correcting the genetic defect but also of introducing unintentional modifications that could have serious implications for the child and future generations — perhaps even more serious than the one that should be prevented. The proportionality of potential benefits and risks differs with regard to the aim of the intervention. Before the technology can be proven "safe enough", also only in biomedical terms a lot of research is required. Specific to this kind of research is that hundreds and thousands of human embryos may have to be used and discarded. This alone is ethically condemned and illegal in some Member states, whereas others allow research on embryos up to 14 days of their development.

Some scholars also hold that this research is ethically required in order to prevent harm for future children through disorders that could possibly be avoided. However, in view of the EU subsidiarity principle governing legislation on human embryo research, the EGE holds back with a recommendation on this issue. There are a number of values and concepts and value-laden criteria that determine what kinds of risks and what level of probability and severity of a harm may challenge the "safe enough" criterion. Libertarian theories are in favour of "procreative beneficence", justifying even a risky intervention if it is intended to provide the best possible conditions for the child and acknowledging its parents' reproductive self-determination [26]. Other theories, in contrast, defend the right of the child to be born without any intentional genome editing [27].

Another central proportionality question is posed by the availability of technological alternatives to genome editing for avoiding heritable disorders, such as preimplantation genetic diagnosis and donation of gametes (yet, those raise other ethical questions). Only few reproductive constellations exclude all strategies but genome editing to ensure that a child is born without a disorder. This is the case, for example, if both parents are carriers of two alleles of a recessive disorder, so that every embryo

can only inherit disease-causing alleles. Are research on embryos and the risk of harm caused by the technology ethically acceptable and proportionate for the few cases for which there is no alternative?

Another ethical challenge consists in the scenario of some children being born with technologically induced disorders because the technology is, at some point, meant to be safe enough and put forward to clinical studies. Some see this as an instrumentalization of these embryos and children, thus violating their dignity. In any such case, life-long and multigenerational monitoring would be necessary in order to gain insight into long-term effects on the biological, psychological and social level.

Which implications and risks would these life-long studies mean for the person concerned and their relatives and social environment? In light of the variety of ethical challenges posed by heritable human genome editing, inclusive societal debate is necessary. A broad societal consensus is precondition for the reproductive use of human genome editing to be considered.

Societal engagement with it must be well-informed and be based on an awareness that the accumulation of individual choices, as also elicited by competitive societies and hidden (or not hidden) market forces, could result in heritable human genome modification that may change the society itself. Public engagement should involve a range of publics, scientists, scholars in the social sciences and humanities, ethicists, legal and policy specialists, and other experts, organised civil society, with special attention to representatives of women's rights, rights of the child, gender equality, social equality, reproductive rights and justice, disability rights, and human rights in general.

The EGE supports the initiative to found a Global Genome Editing Observatory for the purpose of hosting such a debate and recommends that an affiliated European platform be instituted. In fact, "safety" does 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 [2, p. 34-36]. A specialised body in the EU that would assess the risk on case by case basis in genome editing of humas, license other bodies to conduct a quality research and also host a debate on genome editing seems to be necessary. This body may have different task and ideally it would be created by the EU with competences in all EU Members.

Conclusion. The Opinion results in recommendations. EGE issued general recommendations on overreaching matters and concerns. Notwithstanding the rules of The EU Directive 98/44/EC on the legal protection of biotechnological inventions that specify which inventions are patentable based on ethical reasons and which are not, EGE issued recommendations of universal character. EGE took into account the basic principle of the directive such as, patentable inventions include biological material that is new, involves an inventive step, and is industrially applicable. The directive also sets out exceptions to patentability, such as plant and animal varieties, essentially biological processes for the production of plants and animals, the human body at various stages of its formation and development, and processes for cloning humans.

These recommendations mostly highlight the tools and issues debated in past and throughout the Opinion. General recommendations focus on a broad and inclusive societal deliberation on genome editing, avoiding narrow conceptualisations on ethics and governance of genome editing, and developing international guidelines and strengthen governance tools. The general recommendations may be perceived as general starting point for all areas of genome editing. When EU Members wish to address ethics of genome editing in its entirety, they should consider these starting points contained in general recommendations. When EU Members consider a specific ethics of genome editing, they should turn to specific recommendations.

EGE issued separate recommendations for ethics of genome editing in plants, animals, and humans. These specific recommendations seem to be of a greater importance because it provides tangible guidance on how ethics on genome editing are currently shaped in each area.

Generally, we may divide specific recommendations into four groups. The first group recommends the public debate and sharing information on genome editing in all areas, for example recommendation "pay more attention to public debates about genome edited agricultural products" or "engage in global governance initiatives and create a platform for information sharing and inclusive debate on germline genome editing". The second group recommends a legal regulation or governance by an official body such as "regulate the banking and farming on animals carrying human organs for transplantation" or "ensure adequate competencies in expert bodies" for genome editing in humans. The

third group recommends creating a public registry for information on genome editing such as "establish a public registry for research on germline genome editing" or "investigate mechanisms for traceability and labelling of genome edited crops". The fourth group is specific because it contains specialized recommendations tailored to a natural issue of plants, animals, or humans. Within genome editing in plants, specialized recommendations are for example to develop mechanisms to ensure corporate responsibility or develop measures to support small actors that deal with a specific unbalance between corporate bodies and farmers.

The ethics of genome editing in animals bring specific recommendations such as "broadly discuss the humanisation of animals and implement appropriate limitations" or "prevent unregulated use of genome editing tools". Also, within ethics of genome editing in animals we can identify a subgroup dealing with farm animals, where the ethical concerns are "ensure the wellbeing of genome edited livestock animals" and "reconsider ethically contested industrial farming practices". A very specific and controversial ethical issue, enhancement and de-enhancement of humans, is addressed in the recommendation "protect social justice, diversity and equality".

Besides the different ethical recommendations that solely ponder on each area or a separate aspect of ethics, we can identify ethical denominators typical for every researched area, such as the analysis of cost and benefits of genome editing. There is the recommendation to develop an (eco)systems approach for evaluating the costs and benefits of genome edited crops, where 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.

Similarly, 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 in animals. In humans, 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.

The fact that the EGE embarked on the cost and benefits analysis in all areas signals that the Opinion reflects also practical aspects of genome editing which may be of high importance in the future. Another common denominator is a regulatory framework. Although, it is crystal clear that genome editing in all areas must be precisely regulated by governments, there is a difference in the quality of such regulation. While, according to the Opinion, the regulation of genome editing in animals should be firm, regarding plants, 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.

The establishment of standards is typical for 2 areas, ethics of genome editing in animals and humans. The EGE calls for the formation of standards. In genome editing in humans, the EGE advocates 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. Also, the EGE suggests that official bodies should ensure high-standing and consistent application of ethical standards in genome editing in humans. Moreover, strict standardisation is recommended in ethics of genome editing in animals in the case of experimentation with non-human primates.

The ethics on genome editing in plants reflects several key factors. The ethics acknowledge 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. In the light of potentially beneficial impact of new varieties, the EGE also calls for the cost analysis, soft regulation and includes the responsibility of private companies. The EGE suggests creating an EU system of traceability and

labelling only for new varieties where the modification could not have occurred naturally through mutation or natural recombination with sexually compatible plants. In this fashion, the EGE also proposes that the EU Commission should investigate the use of patent registers as a method of identifying genome edited plants. The EGE also acknowledges the possible struggles of small actors such as high cost of risks assessments and imposed regulations. In the case of small actors, the EGE considers measures of supporting 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. Lastly, there is also recommendation to engage public in informed debate on GMOs products.

While ethical issues of genome editing in plants focus on its impact on humankind and practical aspects of harvesting GMOs plants, ethical issues of genome editing in animals focus on guaranteeing good standards of animal lives and the relationship between humans and animals. How do we see animals? Do we perceive them living and breathing beings with certain rights? This fundamental question is in the centre of ethics. The EGE calls for a careful monitoring of the impact of genome editing techniques on the implementation of the 3Rs, evaluation cost/benefits and ensuring transparency, sharing of data and tissues, and the publication of negative results in order to minimise uncoordinated duplication of experiments. Regarding the experimentation with non-human primates, EGE finds it 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. Also, the additional R is recommended — Recourse to alternative strategies in experiments with NHPs and experiments where animal genes are modified by human phenotypes ought to be registered in a public database under the responsibility of a public authority. EGE highlights the importance of broad discussion on humanisation of animals, the strict regulatory framework for animals carrying human organs for transplantations, prevention of unregulated genome editing and risks of de-animalisation. The ethics of genome editing towards livestock animals focus on the health and wellbeing and farming practices.

The recommendation in the Opinion regarding ethics on genome editing in humans are surprisingly realistic and practical. The common opinion on genome editing in humans is very well know, it is a refusal of it. Regarding refusal there is an interesting twist, it seems that in the case of prevention and therapy, the view has begun to change. It seems that genome editing in humans while used for the prevention and therapy may be more acceptable ethically than enhancement of human body as a result of genome editing. The EGE reflects this shift in ethics by encouraging global initiatives and calls for the creation of a European Platform to facilitate exchange of information and open public debate on ethical and social implications on germline genome editing. According to the EGE awareness should be raised about the implications if widely used terminologies and distinctions, such as those between somatic and germline editing or between prevention, therapy and enhancement. The EGE also propose to create 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. The EGE recommends establishing 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 [2, p. 86-87].

The EGE realise the potential of enhancement to foster social inequality and disruption of diversity. To this end, the EGE recommends to proactively safeguard against enhancement or de-enhancement of traits and to ensure that investments in research on germline genome editing have the purpose of protecting health. 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". 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 [2, p. 87-88].

The EGE admits that genome editing technologies are evolving quickly and the law must keep up. Therefore, 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 [2, p. 88].

Although there is a respected principle of subsidiarity on genome editing among EU Members, there a need for an official specialised body with broad competences that would oversee research, assessments in each case of genome editing and public debate. This official body may be more effective than proposed platforms. Ethics on genome editing in some areas such as improving plants for better food distribution or on case of prevention and therapy may shift towards to the acceptance of it. The ultimate obstacle towards balanced and informed debate on ethics of genome editing is a noticeable lack of research. The research in genome editing should the utmost aim of the EU.

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ПРАВОВІ ТА ЕТИЧНІ ПРИНЦИПИ РЕДАГУВАННЯ ГЕНОМУ В ЄС

За останнє десятиліття біотехнологічні винаходи значно розвинулись, породжуючи різноманітні етичні проблеми. Ця стаття присвячена етиці редагування геному в Європейському Союзі. У ній розглянуто погляди Європейської групи з питань етики та їхній потенційний вплив на біотехнологічні винаходи. Дослідження розділено на чотири розділи: у першому пояснено методи редагування геному та наскрізні етичні аспекти; другий стосується етичних питань у редагуванні геному рослин; в третьому описано етику щодо редагування геному тварин; а в четвертому здійснено аналіз етичних міркувань стосовно редагування геному людини. У висновках оцінено поточні етичні питання редагування геному в ЄС на основі рекомендацій Європейської групи з питань етики.

Редагування геному є делікатною темою, яку широко обговорюють уряди, науковці та громадськість. Дискурс був пожвавлений новими технологіями, які обіцяють суспільні вигоди, але викликають юридичні та етичні питання. Як правило, патенти, пов'язані з редагуванням геному, заборонені в ЄС через етичні міркування. У статті розглянуто висновок щодо етичності редагування геному, виданий Європейською групою з етики, незалежним дорадчим органом Європейської комісії. Стаття побудована так, щоб надати вичерпний огляд етичних питань, пов'язаних із редагуванням геному, включно з термінологією, методами та впливовими аспектами, такими як мова, природність, людяність, різноманітність, безпека та управління.

Етичні питання редагування геному в рослинах зосереджені на модифікації рослин, створенні нових сортів рослин, питаннях безпеки, ідентифікації генно модифікованих організмів, біорізноманітті, індустріалізації сільського господарства, біозахисті, справедливості та суспільних міркуваннях. Стосовно тварин етична дискусія побудована навколо інструментального використання відредагованих геномів тварин для блага людини, добробуту тварин, упровадження 3*R* (*Replacement, Reduction, Refinement* — заміна, зменшення, удосконалення), гуманізації та біорізноманіття. Етика редагування геному у людей є найскладнішою, якщо брати до уваги фундаментальні концептуальні міркування, безпеку, гуманність, природність, різноманітність, відмінність між терапією, профілактикою та покращенням, а також критерій «досить безпечно».

Стаття завершується рекомендаціями Європейської групи з питань етики, де наголошено на необхідності широких суспільних обговорень, правового регулювання, державних реєстрів і підтримки менших учасників. Рекомендації підкреслюють важливість балансу між етичними міркуваннями та практичними аспектами, такими як аналіз витрат і вигод, нормативно-правова база. Кінцевою метою є сприяння поінформованому та збалансованому обговоренню етики редагування геному, підкріплене всебічними дослідженнями та управлінням.

У статті розглянуто правові питання, пов'язані з редагуванням геному в ЄС. Обговорено заборону патентування біотехнологічних винаходів, заснованих на редагуванні геному, проаналізовано вплив етичних аспектів на законодавство у сферах патентів і біотехнологій. Особливу увагу приділено правовому статусу людських ембріонів, законам про експерименти на тваринах і регулюванню генетичних модифікацій у контексті біорізноманіття та біоетики.

***Ключові слова**:* правовий статус людських ембріонів, законодавство про експерименти на тваринах, редагування геному, етика, біотехнологічні винаходи, Європейська група з етики, біотехнологія, етичні міркування, генетична модифікація, біорізноманіття, біоетика.