OPINION 133

ETHICAL CHALLENGES OF GENE EDITING: BETWEEN HOPE AND CAUTION

COMITÉ CONSULTATIF NATIONAL D'ÉTHIQUE
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SUMMARY

Genome engineering has for decades been a key driver of understanding and more recently has seen major advances that have led to gene editing.

Current disruptive innovation is twofold: implementation of increasingly rapid genome sequencing techniques and development of more and more efficient tools for the editing of existing DNA sequences, for rewriting of the genome, as it were. These unprecedented biotechnological tools promise to shed light on the role of genes, the significance of variations between individuals, notably regarding their state of health, and, more generally, new possibilities for human genome repair and for the domestication of plants and animals better suited to human needs.

The applications of these technologies to living organisms, including humans, nonetheless raise concerns and prompt ethical reflection on the transmission of genetic modifications to future generations. The ethical questions also relate to our currently imperfect control of the techniques used and to the uncertain short- and long-term effects on individuals and on ecological and evolutionary systems.

In the plant world, crosses between varieties, methods of selection, techniques of in vitro multiplication, mutagenesis, transgenesis, and recently gene editing have enabled the adaptation of certain plants to human needs, while raising societal, ethical, and intellectual property issues.

In the animal world, several applications are being developed to introduce deleterious genes into harmful species so as to eradicate them or, in contrast, to introduce resistance genes into populations of species threatened by bacterial, fungal, or viral infections. The long-term effects of these applications on the ecosystem are, however, totally unknown. In animal breeding, experimental procedures to amplify the classic approaches to genetic modification of livestock have long been applied for the purposes of commercial profitability, but neglect the question of animal welfare. Even more problematic is gene drive, which enables the rapid introduction of genetic modifications into a whole population. In the public health context, the use of gene drive to control vector-borne diseases by, for instance, eliminating species like malaria vector mosquitoes, may have uncontrollable and possibly dire consequences.

In humans, clinical trials of modification of the genome of somatic cells seem promising in various fields. However, the new possibility of editing the human genome not in somatic cells but in gametes or embryos means that all the cells of the body, including the germ cells, are affected, and this poses a major ethical problem because of transmission of genetic modifications to future generations.

This approach is banned in France outside the field of basic research because it contravenes the Oviedo Convention, which was ratified by France, and article 16-4 of the French Civil Code.

Whereas international authorities have established legal safeguards, the corresponding texts have not been unanimously ratified, including in Europe.

The ban on human gene editing involving transmission of genetic modifications to future generations was recently flouted in China, with the result that twin girls with edited genomes were born. This experiment was strongly and unanimously condemned worldwide, including by the CCNE[1]. This event reinforces the need for a legal framework rooted in ethical reflection both nationally and internationally.

It is important to emphasize the responsibility of researchers and scientific institutions in applying research findings to humans, given the risks inherent to the implementation of gene editing and the attendant hopes. Thus, the legal and regulatory frameworks derived from bioethics laws and the Oviedo Convention, for example, should always be explicit and precise in the professional fields concerned and should also be the subject of public debate.

In the present opinion, the CCNE defines four principles and perspectives:

1. Laboratories doing basic research involving the new techniques of gene editing should be encouraged. Whatever the relative ease of their implementation, it is important to develop experimental approaches to make these techniques safer, even reversible, and to regulate their application to living organisms.

2. The applications of gene editing to non-human living organisms are an undeniable source of potential benefits. However, thought should be given to animal welfare and to possible uncontrollable, even dire consequences, like disruption of ecosystems and evolutionary systems. For example, in the control of vector-borne diseases, genome editing, especially when associated with gene drive, may well have the opposite of the desired effect: the emergence of new potentially more dangerous disease vectors. The organisms concerned should only be released from laboratories after systematic and meticulous evaluation of the potential risks, and even following implementation of measures enabling reversibility and continuous monitoring. It also seems essential to consider plants, fungi, and animals with edited genomes as genetically modified organisms.

3. In somatic gene therapies, human gene editing constitutes medical progress and should be supported. Ethical reflections remain but, because modifications introduced in the patient are not passed on to the next generation, such treatments should be considered like any other gene therapy.

4. Because of the extent of the technical and scientific uncertainties associated with the short- and long-term effects of modifications to the human genome that are passed to future generations, above and beyond French legislation, an international moratorium should be imposed before any implementation. These technical and scientific uncertainties, even if

[1] https://www.ccne-ethique.fr/fr/actualites/communique-de-presse

reduced, would remain the main ethical question of an individual treatment that is not part of a eugenic attempt to transform the human species.

So, advances in genetic knowledge enable, among other things, the correlation of certain serious and incurable diseases with variations in individual genomes within the human population. The prevention of such diseases at the embryonic stage by genome repair calls for particular ethical reflection regarding care that could become a medical procedure in the future.

PREFACE

The modification of genomes* by genome engineering* has for decades been a key driver of knowledge, although the short- and long-term consequences of such modifications remain unknown or poorly understood. Specifically, the genome of cultivated plants, crosses between varieties, methods of selection, and the techniques of in vitro multiplication, mutagenesis* and transgenesis* have progressively enabled the adaptation of certain plants to human needs, taking into account the environmental context, while raising societal, ethical, and intellectual property issues.

Current disruptive innovation is twofold: implementation of increasingly rapid genome sequencing techniques and development of more and more efficient tools for the editing of existing DNA sequences, for rewriting of the genome, as it were. These unprecedented biotechnological tools promise to shed light on the role of genes*, the significance of variations between individuals, notably regarding their state of health, and, more generally, new possibilities for human genome repair and for the domestication of plants and animals better suited to human needs.

These disruptive innovations and their attendant scope also generate questions and fears[2] and lead to questions notably regarding desirable changes in bioethics laws, as indicated by the CCNE's Opinion 129[3], which was used to prepare the present opinion and was the CCNE's contribution to the États généraux de la bioéthique (Bioethics Forum) in 2018.

Ethical reflection on modification of the human genome is not new. It began in the 1990s with the advent of somatic gene therapies* and grew from 2010 with the rapid development of gene editing techniques, which were, however, hard to implement at the time. Human and non-human gene editing, which now seems precise, targeted, and easily achievable, justifies an analysis of the benefits in light of the risks to humans and ecosystems.

The current breadth of ethical reflection stems not only from the fact that it has become increasingly easy technically to modify the genomes of individuals and of plants and animals, but also from the fact that edited genomes are transmitted to future generations. These developments may have complex consequences that are in part unforeseen or even harmful to ecosystems.

In humans, such a technological approach that alters the germline is currently outlawed, except in basic research, because it contravenes the Oviedo Convention (1997) and Article 16-4 of the French Civil Code.

[2] J-Y Le Déaut and C. Procaccia (2017). Les enjeux économiques, environnementaux, sanitaires et éthiques des biotechnologies à la lumière de nouvelles pistes de recherche. OPECST, Paris, tome 1, 367p.
[3] https://www.ccne-ethique.fr/sites/default/files/publications/resume_avis_129_-_en_anglais_2012_v6.pdf

Limits in this field have been set by international organizations (WHO, UNESCO, Council of Europe), which have identified legal safeguards, but the corresponding texts have not been unanimously ratified. The debate has, moreover, become more heated since 2015-2016, following the publication by several teams (in China in 2015, then in the United States and, more recently, the United Kingdom) of results on the application of CRISPR-Cas9*, a technique for rewriting the genome, to male gametes or to human embryos, albeit only for research purposes. But the red line of implantation of genetically modified embryos was crossed in late 2018 when a Chinese scientist reported using CRISPR-Cas9 to alter the genome of zygotes* and the subsequent birth of twin girls with edited genomes. The scientific community, including the French Académie des Sciences and Académie Nationale de Médecine, unanimously condemned this practice in the current state of knowledge. The CCNE also condemned this experimentation and stressed the need for international governance to regulate these technological developments in its statement of 28 November 2018[4].

These developments consolidate the need for a legal framework on the basis of national and international ethical reflection in this field.

[4] On this subject, other institutions, including INSERM, ARRIGE, the *Académie des Sciences*, and the *Académie Nationale de Médecine*, have issued statements denouncing this clinical experimentation.

INTRODUCTION

In recent years, high-throughput human DNA sequencing has become increasingly affordable and has enabled identification of individual genetic variations in large samples. These variations are interpretable, at least in part, thanks to the development of applied mathematics which by means of computing can process massive amounts of data on large cohorts of individuals. The collection and management of these data raise specific ethical questions that have been examined by the CCNE[5].

In its 2016 Opinion 124, "Ethical Reflection on Development in Genetic Testing in Connection with Very High Throughput Human DNA Sequencing", the CCNE examined ethical questions on the huge growth in DNA sequencing capacity and analyzed the significance of the variations observed in individuals, without forgetting that the complexity of a living organism is not based on its gene sequence alone.

Individual genetic variations can be single nucleotide changes with no detectable pathological effect, in so-called genetic polymorphism. However, some of these variations, when classified and correlated with agronomic, zootechnical, or clinical data, can be considered as directly associated with or predisposing to traits to be selected in animals or plants, or with genetically transmitted disease in humans. In the latter case, some of these constitutional genetic variations may be related to well-identified hereditary diseases. Acquired in certain cancer tissues, these variations may lead to new therapeutic indications, immuno-oncological, for example. In pharmacogenomics, these variations enable identification of sequences associated with pharmacological sensitivity and hence guide therapeutic practices[6].

The determination, the desire, even the need to use these techniques in various fields, notably in humans, in the identification of people, genealogy, public health, and precision medicine, should not obscure the fact that before opening the way to predictive medicine, the greatest challenge of modern genetics is that of knowledge, and hence of research.

In terms of this research, the development of increasingly efficient innovative tools has allowed editing of existing DNA sequences, thus promoting the development of genome engineering in living organisms. Genome engineering has for decades been a major tool in enhancing knowledge. Gene editing in vitro in a given cell or in vivo in a strain of laboratory organisms enables precise analysis of the role of the protein encoded by this gene[7]. This is an essential research tool that is irreplaceable in our search for greater understanding of

[5] CCNE Opinion 130.

[6] Inappropriately called "personalized medicine."

[7] However, the strains modified in this way are not supposed to be released into the environment before the modification is shown to be harmless to humans and to ecosystems and before analysis of its possible transfer to other species. In Europe, applications, notably in agribusiness, have observed these regulations for over ten years now.

physiological and pathological phenomena, and of the genome itself[8]. The use of gene editing in basic research leads to major advances and should therefore be supported in the laboratory, regardless of whether or not there is an immediate prospect of application.

Recently, the advent of a new technique, called CRISPR-Cas9, has led to the crossing of a new threshold, as the "genome surgery" enables it as much easier to perform, in peculiar technically and economically. It is based on the capacity of some bacteria in the natural state to defend themselves against viruses by using the enzyme Cas9, which "cuts" the viral genome. The technique of genome editing using the enzyme Cas9 was first applied to mammalian cells in 2012 by Jennifer Doudna (UC Berkeley, United States) and Emmanuelle Charpentier (Umeå University, Sweden)[9], and then to human cells by the molecular biologist Feng Zhang of the Broad Institute (Cambridge, United States). This technique consists in introducing into a cell the endonuclease Cas9, which recognizes particular DNA motifs (CRISPR motifs) and is able to cut the DNA at an extremely precise point thanks to a guide RNA*, determined by the experimenter as specific to the targeted gene. However, the repair of this cut is, currently, only partially controlled and does not permit the exclusion of the appearance of unwanted DNA sequences. A more recent advance based on the same technology of recognition of certain CRISPR motifs, but replacing the endonuclease Cas9 by Cas13, means that it is not the genome that is modified but the RNA (and by extension, the resulting protein) in mammalian cells. This approach could be essential, not only in research, but also in human therapeutics, for example by inactivating the RNA coding for a protein with a dominant negative effect, without modifying the genome[10]. New experiments even suggest the possibility not of cutting a fragment of DNA or RNA, but of modifying only a single base (prime editing) , thus opening the way to the correction of numerous genetic diseases caused by a point mutation*.

The development of tools enabling manipulation of the genomes of individuals and of populations, in a context where we have incomplete knowledge of genome functioning and evolution, further fuels ethical reflections given that some of these manipulations can be performed outside research institutions, because they are technically easy to implement. In parallel, the evolution of technical tools for genome editing raises questions also posed in other areas of human health, because the development of some medical techniques

[8] This question of the modification of the genome was the subject of the CCNE's 1990 Opinion 22 on gene therapy, in which the CCNE, among other things, took "*a favourable view of human research [...] provided the following conditions are observed: - gene therapy should be restricted in its scope to somatic cells, and there should be a formal prohibition of all attempts to deliberately modify the genome of germinal cells, and of any gene therapy involving the risk of such a modification. [...] in the area of hereditary diseases, gene therapy research must only be considered for diseases resulting from an anomaly concerning a single gene (monogenic diseases), and that produce a particularly severe pathology*."

[9] Jinek M et al. (2012). A programmable dual-RNA-guided DNA endonuclease in adaptive bacterial immunity *Science*. 337(6096):816-21

[10] Abudayyh O. et al. (2017). RNA targeting with CRISPR-Cas13. *Nature*. 550:280-284

generates tension between individual aspirations[11] and collective visions, which can pose problems on a global scale that in time can lead to "medical tourism" and above all to eugenics*[12].

This new capacity for intentional and targeted editing of the genome, including the germline genome of all species, humans included, raises ethical questions regarding the human species and other species in the natural world. Depending on the case, rewriting of the genome in animals and plants has health or commercial purposes, but the expected benefits of the gene editing of such and such a species cannot conceal the potentially harmful and in part unforeseen effects on biodiversity, given that our knowledge is at present limited and that natural biological evolution is unpredictable.

In humans, wanting to match the genome of unborn infants to familial or societal expectations includes the worthy aim of eliminating diseases, but can also lead to a eugenic approach that should be proscribed and examined, including in protocols for somatic modifications.

The increasingly straightforward implementation of these methods therefore underscores the importance of the ethical debate, particularly on the introduction of genes into a species that does not have such genes and the transmission of genetic modifications to future generations. In these two cases, we should keep in mind the preservation of ecosystems, globally and genetically, and remember that "*the human genome is not the property of any particular culture, nation, or region; still less is it the property of science alone. It belongs equally to every member of our species, and decisions about how far we should go in tinkering with it have to be accountable to humanity as a whole*"[13].

So, the ethical reflections in the present opinion are intended to generate debate around attempts to reconcile efforts to understand the genome and its functioning with avoidance of abuses related to, among other things, the fact that some of these genetic modifications can be transmitted to future generations. These reflections concern the future of humanity in terms of technical and medical possibilities and have become all the more pressing since the announcement of the birth of genetically modified twin girls: what is socially desirable, and what in the general interest should be implemented, postponed, or banned?

[11] Such aspirations may, for example, involve ethical reflections related to the wish to have children that are considered in the CCNE's Opinion 126, in addition to questions of choice of the child's genetic characteristics, ranging from the correction of an incurable hereditary disease to the increase of certain traits according to clearly eugenic, transhumanist agendas. To avoid creating immediate and longer term inappropriate expectations, society should not foster a simplistic vision of the genome. The genome cannot be reduced to the juxtaposition of genes deemed *a priori* to be "normal" or "abnormal".

[12] In areas as different as medical tourism and the perturbation of ecosystems, problems of international governance are added to those of information, debate, and societal choices.

[13] Jasanoff, S., J. B. Hurlbut & K. Saha (2015). CRISPR Democracy: Gene Editing and the Need for Inclusive Deliberation. *Issues in Science and Technology.* 32, no. 1.

SOME ETHICAL PRINCIPLES AS BENCHMARKS FOR REFLECTION

Basic ethical reflection consists in determining whether the fact that a new technique makes possible something that was not possible before alters the nature of ethical inquiry, or whether it only modifies the degree of urgency. Thus, "should we modify the human genome?" is not a new question. It was asked in the 1990s upon the advent of non-targeted somatic gene therapies and became even more pressing in 2010 with the rapid development of gene editing techniques, which were, however, hard to implement at the time.

Human and non-human gene editing today is precise, targeted, and easy to implement, and so there is a need to analyze its reputed benefits in light of the risks to humans and to ecosystems.

Biomedical ethics has developed since the 1970s, and learned societies have sometimes envisaged moratoria on research and scientific techniques likely to alter the germline genome, in humans and in all living organisms (eukaryotes and prokaryotes)[14]. In 1979, the Belmont Report[15] specified what gives meaning to actions in the life sciences and healthcare, through simple principles in the diagnosis and treatment of diseases and in scientific research. This is now applicable to gene editing. The report recommends that such actions should:

- not harm individuals or society at large;
- be relevant and state-of-the-art, and minimize the risks involved;
- respect the autonomy of the person, who must be a stakeholder in medical or scientific decision making in the context of informed consent;
- have as an essential aim individual and/or collective beneficence;
- observe the principles of justice, fairness, and solidarity.

Beyond basic research, these advances constitute progress in terms of applications to living organisms, including in human clinical studies by opening up new perspectives for the treatment of serious and incurable genetic diseases. At the same time, the new possibilities of altering the germline genome raise major ethical questions, which are all the more pressing given that a red line was recently crossed with the birth of genetically modified children, as mentioned in the CCNE press release of 28 November 2018. Moreover, the ethical debate is pressing because the relative simplicity of use of gene editing techniques allows their worldwide application, including in medicine, in institutions that are not necessarily subject to ethical principles and which may even have purely commercial aims.

[14] Deliberation on the need for and limits of moratoria continued, from the Asilomar Conference in 1975 to the UNESCO International Bioethics Committee 2015 report: unesdoc.unesco.org/ark:/48223/pf0000233258
[15] Ethical Principles and Guidelines for the Protection of Human Subjects of Research (18 April 1979).

Genome editing techniques, particularly those that use CRISPR-Cas9, have developed apace in several laboratories and companies in the developed world. These techniques heighten questioning regarding not only the transmission of genetic modifications, but also the individual and social expectations they engender.

Reflection has notably focused on expanding what is possible by prioritizing the immediate biotechnological goals of treating diseases, rather than an overall vision of human health. This form of reflection highlights the potential, precision, and ease of implementation of these biotechnologies, and even creates markets. The notion that we can outdo nature, because we can work faster and according to a rational design, has a long history.[16]

From an ethical perspective, we should instead test the relevance of rapidity, and notions of time and temporality, by considering the coevolution of the human species in the living world. In its Opinion 125, the CCNE emphasizes: "*the difference in the timescale of a human life, or even of humanity, and the timescale of nature being totally beyond comparison, perhaps even inconceivable. Seen from a human perspective, evolution has never "hesitated" to eradicate certain forms of life, whole species even, that it had once created, as the various surges of massive extinction attest. While such events have never come close to eradicating life on earth, they have weighed very heavily on its history and, among other things, on the emergence of our species. Today, at a time when biotechnological potentialities appear to be capable of disrupting the balance that the human species has known since its emergence, unprecedented ethical tensions are dawning*".

The relative slowness of changes to living organisms that humans have introduced since the Neolithic age does not absolve us today from thinking about the temporality of our actions and the acceleration of changes made possible by technological advances. With hindsight, this reflection on the temporality of modifications ought to have been anticipated in various areas of biology. Such is the case in the medical and veterinary use of antibiotics, which today has run into the problem of increasingly widespread resistance of pathogenic bacteria. The genomic modifications introduced in agronomy and in the fight against vector-borne diseases must now be analyzed and evaluated in this same temporal context by considering the dynamics of the adaptation of pathogens. Since it now seems possible in the genome of human cell lines "to correct" DNA sequences that cause serious and incurable diseases, some argue that it is "ethically" desirable to do so, omitting however to consider the genomic context and the fact that all genomes present in the biosphere are the result of 3.5 billion years of evolution.

The ethical questions posed by gene editing are not limited to this notion of temporality, but rather raise the question of what sort of world we wish to pass on to future generations, in terms of the environment, biodiversity, and the genetic diversity of humankind. In this context, there is also an ethical requirement to avoid exacerbating inequalities in human social

[16] "*The end of our foundation is the knowledge of causes, and secret motions of things; and the enlarging of the bounds of human empire, to the effecting of all things possible*." Francis Bacon in *New Atlantis* (1627).

development, and to limit alterations in biodiversity while maintaining its evolutionary capacities.

Lastly, rules concerning responsibility, governance, risk management, and public decision making in situations of scientific uncertainty are indispensable to our understanding and acquisition of increasingly complex knowledge. From this standpoint, the scientific community bears a particular responsibility in terms of the ethics and code of conduct of its activities and its transparency with regard to society.

GENE EDITING TECHNIQUES IN NON-HUMAN ORGANISMS

As genome engineering is applicable to all living organisms, this section will describe examples from the worlds of bacteria, plants, and animals.

For several years, bacteria with CRISPR-Cas9, a natural means of defense against infections by bacteriophages[17], have been selected according to the principles of natural selection in the food industry for the fermentation of yogurts and cheeses, as a function of the spontaneous evolution of interactions between bacteria and bacteriophages.
Experimentally, gene editing has been successfully applied to bacteria like *Escherichia coli* and other strains, and to viruses. This represents a major advance in the study of the resistance of bacteria to antibiotics and of their capacity to infect human, animal, or plant cells. However, the use of a technique developed by altering processes that exist naturally in bacterial species must prompt the taking into account, from an evolutionary point of view, of the existence in the natural world of bacteriophages resistant to the endonuclease Cas9 and of inhibitors of Cas9 in certain bacteria[18], and more globally, the significance of the disappearance of this process of mutation during evolution and of its non-inexistence in eukaryotes.
Vigilance is called for, because the gene editing of bacteria or viruses could yield formidable biological weapons[19]. In 2011, an H5N1 virus that is extremely contagious and virulent, because genetically modified to be transmitted among mammals and not only by birds, was developed in the laboratory, even before the advent of CRISPR-Cas9 technology. Publication of the findings of two research teams was initially blocked by the National Science Advisory Board for Biosecurity (NSABB), because of the possible use of the virus in bioterrorism, but the results were subsequently published some months later in the scientific journals *Science* and *Nature*[20].

CRISPR-Cas9 has been used in promising experimental approaches in fungi in the search for and production of medically active substances[21]. Yinong Yang at Pennsylvania State University genetically modified *Agaricus* mushrooms by using CRISPR-Cas9 to disrupt several genes involved in the mushroom's oxidative defense, which is responsible for browning of the carpophore (aerial part of the mushroom) during aging. This technique, which was approved for strictly commercial purposes in April 2016 by the U.S. Department of Agriculture, is applicable to numerous vegetables and fruits. Inactivation of the genes of susceptibility to mildew in potatoes and tomatoes, or of susceptibility to the European corn borer moth, are

[17] Viruses that infect bacteria.
[18] Sontheimer E. J. et al. (2016). Naturally occurring off-switches for CRISPR-Cas9. *Cell,* 167:1829-1838
[19] Clapper J.R. Worldwide Threat Assessment of the US Intelligence Community. (09/02/2016)
[20] Masaki Imai et al. (2012). Experimental adaptation of an influenza H5 HA confers respiratory droplet transmission to a reassortant H5 HA/H1N1 virus in ferrets, *Nature* 486: 420–428.
Sander Herfst et al. (2012). Airborne Transmission of Influenza A/H5N1 Virus Between Ferrets, *Science*, 336, 6088: 1534-1541.
[21] Zheng Y-M. et al. (2017). Development of a versatile and conventional technique for gene disruption in filamentous fungi based on Crispr-Cas 9 technology. *Scientific Reports*, 7:1-10.

advances in agronomy that, among other things, can limit the use of fungicides and pesticides. However, the long-term effects on species, ecosystems, and even food remain unclear and should be monitored continuously.
Reflection is all the more vital because CRISPR-Cas9 technology, by virtue of its ease of use, efficacy, and low cost, enables rapid growth in the use of gene editing in an ill-defined legal and regulatory context. In regulatory terms, there is the question of theoretically undetectable genome modifications produced by CRISPR-Cas9 technology. How then can we guarantee the traceability, for example, of a modified plant, when there is no obligation to document traceability?
The classification of modified plants and fruits as genetically modified crops is a subject of debate in relation to directive 2001/18/EC of the European Parliament and of the Council and the interpretation of its Annex 1A, notably if there is no addition of a gene or nucleotide sequence. In its editorial of 2 October 2018, the journal *Nature* used three research papers on genetic modifications of tomatoes designed to improve their taste to call for less stringent European regulations on their marketing. Using as an example these modified tomatoes, which the editorial considers "appeal" to farmers and consumers, *Nature* argues that the cultivation and commercialization of plants modified by CRISPR-Cas9, including if interspecific gene transfer is involved, should not be subject to the same regulations as conventional genetically modified crops, as such health and environmental regulations hinder the economic development of these products.

This *Nature* editorial echoes and contradicts a previous decision by the European Court of Justice issued on 25 July 2018 (ruling C-528/16) confirming that New Plant Breeding Techniques (NPBT), including the techniques and methods of mutagenesis, and of CRISPR-Cas9, "*alter the genetic material of an organism in a way that does not occur naturally*", and "*that the risks linked to [their] use [...] might prove to be similar to those that result from the production and release of a GMO [genetically modified organism] through transgenesis*"[22].

In this debate, it seems essential scientifically and ethically to analyze as genetically modified crops any plants and mushrooms subject to interspecific gene transfer or to targeted genetic transformation, so as to consider, before cultivating them in the environment, their possible impact on human health and ecosystems, because of lingering uncertainties regarding possible indirect effects.

In its Opinion No. 11 on new techniques for the genetic improvement of plants, the Inra-Cirad-Ifremer joint consultative ethics committee (CCCE) addresses, in addition to the previous

[22] In 2016, this subject generated tension at the French Haut Conseil des Biotechnologies regarding the categorization of various new methods of genetic modification of cultivated plants (termed NPBT), and this had an impact on authorizations for cultivation and consumer information. The Economic, Ethical, and Social Committee (CEES) of the Haut Conseil des Biotechnologies emphasized that "the very existence of a logo covering such a variety of practices raises questions in the context of analysis of the economic, ethical, and social aspects and impacts of these techniques". This subject still divides the scientific and professional community concerned.

reflections, the problem of intellectual property, by reiterating that it can take two forms in Europe: patents or plant variety rights. The latter guarantee the creator copyright, but do not introduce, in contrast to patents, pay-for-access to plants with new genetic traits[23]. While the patent is preferred by the agribusiness sector, the CCCE considers that "*In ethical terms, the plant variety rights system ultimately seems better, insofar as it guarantees both just intellectual recognition and the availability of genetic resources*". The CCCE thus poses a major question in economic, social, political, and ethical terms regarding the intellectual property of transformations of living organisms and the use of genetic resources.

In livestock breeding, several applications are being developed with a view to the transmission of deleterious genes to so-called harmful species so as to eradicate them, or, conversely, to the introduction of resistance genes into species endangered by bacterial, fungal, or viral infections. Other experimental approaches seek to scale up the classic methods of genetic modification of livestock, which have long been applied. Notable examples are the production of hornless dairy cattle using targeted genetic modification, with a view to increasing stocking density by limiting the risk of horn injury among cattle, and the mutation of the gene encoding myostatin, so as to increase muscle mass for reasons of profitability, while overlooking the question of farm animal welfare.
Some play down the importance of the debate on the targeted genetic modification of animals and its risks, arguing that the technique only reproduces, in certain cases, mutations that exist in nature[24]. This argument, on the contrary, warrants special attention and debate on the ethical distinction that should be drawn depending on whether or not the technique allows the complete restoration of an altered gene in the species or the introduction a targeted genetic or epigenetic* modification that does not exist in the natural populations considered, or at least which has never been described in these populations.

In studies of the control of vector-borne diseases, research teams have used CRISPR-Cas9 technology to make malaria vector mosquitoes resistant to infection by *Plasmodium*, with a view to eradicating the transmission of malaria to humans[25]. To take into account resistance associated with the polymorphism of vectors and pathogens, other teams have used genome editing to sterilize female mosquitoes.[26] Experiments are also underway to release genetically modified populations into the environment, so as to transmit resistance genes to an entire local population of Anopheles mosquitoes by gene drive*.

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[23] https://inra-dam-front-resources-cdn.brainsonic.com/ressources/afile/435199-225f7-resource-avis-11-comite-d-ethique-new-techniques-doamelioration-plantes-planche.pdf

[24] Carlson D.F. et al. (2016). Production of hornless dairy cattle from genome-edited cell lines. *Nat Biotechnol.,* 34:479-481.

[25] Gantz V.M. et al. (2015). Highly efficient Cas9-mediated gene drive for population modification of the malaria vector mosquito *Anopheles stephensi*. *Proc Natl Acad Sci USA.*, 112, E6736-E6743.
Dong Y. et al. (2018). CRISPR/Cas9 -mediated gene knockout of *Anopheles gambiae FREP1* suppresses malaria parasite infection. *PLoS Pathog.* 14(3): e1006898. https://doi.org/10.1371/journal.ppat.1006898

[26] Hammond A. et al. (2016). A CRISPR-Cas9 gene drive system targeting female reproduction in the malaria mosquito vector *Anopheles gambiae*. *Nat Biotechnol*., 34:78-83.

So, by introducing targeted genetic modifications homozygously, CRISPR-Cas9 technology circumvents Mendel's laws of sexual reproduction with a view to driving the expression of the modified gene in a whole species within a few generations. In species that reproduce rapidly, gene drive can potentially affect all the individuals of a treated population, even of a species, in a few years. This approach would theoretically allow the eradication of certain species, notably mosquitoes, which spread diseases dangerous to humankind. While gene drives can have a relatively rapid beneficial outcome, the disappearance of a species can have unpredictable effects on the environment[27]: the ecological impact of the elimination of species is still unknown and the adaptation of the pathogen to another, potentially more harmful vector cannot be discounted[28]. Researchers in ecology advocate further studies before the use of gene drive and this and other recommendations have recently been formalized by the Swiss Federal Ethics Committee on Non-Human Biotechnology[29]. The expected benefit of gene drive (for example, the eradication of malaria by introducing into malaria vector mosquitoes a sterility gene or making the mosquitoes unable to transmit the pathogen) should not lead to neglect of other relatively effective approaches, like the draining of standing water, the use of mosquito nets, and vaccination against other vector-borne diseases.

These are ambitious approaches, but their effects on the environment and on long-term health include the emergence of new *Plasmodium*/vector relations, which are likely but unpredictable in terms of the location, temporality, and evolution of vectors. Given current understanding, the probable emergence of forms of resistance should, as with all attempts to control vector-borne diseases, be subject to continuous scrutiny in terms of health, particularly as more generally the effects on ecosystems are currently unknown[30].

Gene drive has greatly contributed to concerns associated with the use of genome editing technologies in the natural world, and at the 2015 United Nations Climate Change Conference (COP21) experts from around the world launched a moratorium to limit their use. In order not to curb their use in research, the US National Academies of Sciences, Engineering, and

[27] Barret P. et al. (2016). Ėthique et biodiversité : questions posées à et par la recherche agronomique. https://www.cairn.info/revue-natures-sciences-societes-2016-3-page-270.htm

[28] Information should be increased when taking into account the populations immediately concerned, by telling them that the method acts on future generations of the vector, not on the generation that is transmitting the pathogen in the here and now, and cannot therefore respond to epidemic situations constituting health emergencies. In the same spirit, because of the capacity for adaptation of vectors and pathogens, this approach, like all approaches to the control of vector-borne diseases, requires continuous monitoring of populations of vectors and pathogens and can only be meaningful as part of an overall health plan.

[29] Gene drives – Ethical considerations on the use of gene drives in the environment. Report by the ECNH, August 2019, 10 p.

[30] In the present context of scientific uncertainty, technological improvements may enable a response to the detection of unexpected toxicity of the endonuclease in certain mosquitoes in the large population samples of bred mosquitoes and to the appearance of untargeted mutations in modified species. But, in the natural world, the risks of within- and even between-species transmissions, technological considerations apart, should be a permanent reference which, as emphasized by CCNE Opinion 125 on the relationship between humanity and the living world, cannot be based on mistaken aims or even claims to control everything.

Medicine published in 2016 a series of recommendations[31], with a view to promoting responsible quality research that takes into account the potential consequences for the ecosystem and the possibilities of misuse (bioterrorism, for example). To achieve this, the National Academies recommended transparent research including sharing of data and knowledge.

As a remarkable research tool, gene editing generates new understanding of the genome and even new perspectives in terms of the development of animal models, particularly rats and mice, for the study of various diseases. Elimination of porcine endogenous retroviruses dangerous to humans[32] or of immunogenic sugar moieties by CRISPR-Cas9 could justify new boom in research on xenografts and animal chimeras containing human elements, while renewing the importance of specific ethical reflection on the creation of animal-human chimeras.

- Laboratories doing basic research involving the new techniques of gene editing should be encouraged. Whatever the relative facility of their implementation, it is important to develop experimental approaches to make these techniques safer, even reversible, and to regulate their application to living organisms.

- The applications of gene editing to non-human living organisms are an undeniable source of potential benefits. However, thought should be given to animal welfare and to possible uncontrollable, even dire consequences, like disruption of ecosystems and evolutionary systems. For example, in the control of vector-borne diseases, genome editing, especially when associated with gene drive, may well have the opposite of the desired effect: the emergence of new potentially more dangerous disease vectors. The organisms concerned should only be released from laboratories after systematic and meticulous evaluation of the potential risks, and even following implementation of measures enabling reversibility and continuous monitoring. It also seems essential to consider plants, fungi, and animals with edited genomes as genetically modified organisms.

[31] *Gene Drives on the Horizon: Advancing Science, Navigating Uncertainty, and Aligning Research with Public Values.* (2016). Committee on Gene Drive Research in Non-Human Organisms. National Academies of Sciences, Engineering, and Medicine http://www.nap.edu/23405

[32] Niu D. et al. (2017). Inactivation of porcine endogenous retrovirus in pigs using CRISPR–Cas9. *Science,* 357:1063-1067.

GENE EDITING TECHNIQUES IN HUMANS

The technical uncertainties inherent in genome editing, in the general context of partial understanding of genetic regulation, have until recently prevented its application to the human germline. In contrast, the genomes of somatic* cells have been successfully edited with a view to treating several diseases. In 2009, a technique[33] for somatic genome editing was used in a clinical trial in 12 patients infected by HIV (human immunodeficiency virus). The researchers built on the observation that carriers of a spontaneous mutation of the gene coding for CCR5, an HIV co-receptor, were protected against infection by this virus. They specifically introduced this mutation into the sequence of the *CCR5* gene of the T cells of infected patients, and then re-introduced these HIV-resistant lymphocytes into the patients, to prevent later reinfection and destruction of lymphocytes. Since 2009, more than 20 clinical trials have been conducted or are ongoing using various genome editing methods, 7 of them with the same aim as above, including one trial targeting hematopoietic stem cells for long-term treatment[34].

More recently, with the advent of gene editing techniques such as CRISPR-Cas9, a step forward has been taken with their application to germ cells, resulting in genetic modifications that are transmitted to future generations.

Gene editing, when applied to the genome of somatic cells, opens up prospects of progress in human therapeutics (cell therapy with hematopoietic stem cells or genome-edited induced pluripotent stem cells* from the patient him/herself, treatment of cancer, treatment of certain viral infections ...). Twelve clinical trials are under way, notably in China and the United States. They are using genetically modified T cells to fight against tumors (lung, melanoma, myeloma) or viral infections (inactivation of the CCR5 receptor in HIV infection[35], as mentioned above), as well as genetically modified hematopoietic stem cells in the treatment of two blood disorders: sickle cell disease and β-thalassemia. The recent treatment of Duchenne muscular dystrophy in a canine model by somatic gene therapy using CRISPR-Cas 9 technology, if the results are confirmed, will raise great hope in terms of the treatment of certain human inherited diseases[36].

Such gene editing, even somatic, nonetheless raises no more ethical questions than those in part referred to in 1990 in the CCNE's Opinion 22 on gene therapies, and then addressed in other more recent opinions. The CCNE already opposed any modification of general physical (height, for example) or mental (behavior) genetic characteristics in the field of hereditary diseases, writing that "*gene therapy research must only be considered for diseases resulting*

[33] Genetic engineering with zinc-finger nucleases: the principle is the same as that of CRISPR-Cas9 technology, but its application is less effective.
[34] Porteus M. H. (2019). A new class of medicines through DNA editing. *NEJM*. 380 (10): 947-958.
[35] Baylis F. & M. McLeod. (2017). First-in-human Phase 1 CRISPR Gene Editing Cancer Trials: Are We Ready? *Curr Gene Ther*.17 (4):309–319.
[36] Amoasii L. et al. (2018). Gene editing restores dystrophin expression in a canine model of Duchenne muscular dystrophy. *Science*, 362 (6410):86-91.

from an anomaly concerning a single gene (monogenic diseases), and that produce a particularly severe pathology."

Genetic modification of somatic cells reprogrammed as induced pluripotent stem cells also holds promise as a future therapeutic tool for some diseases. Somatic cells reprogrammed to pluripotency acquire the potential to differentiate into any cell of the body, including primordial germ cells. This technique, by altering the classic distinction between germ and somatic cells, brings the ethical debate to bear on all genetic modifications that are transmitted to offspring, regardless of the technique used. It has, in fact, become possible today to derive primordial germ cells, even gametes (spermatozoa and oocytes), from these somatic cells and so to alter the genome of the resulting germline[37]. This can be beneficial in the treatment of certain infertilities, but also raises a risk that should be analyzed by distinguishing between curative genome editing and eugenic misuse[38].

With the advent of gene editing techniques, one major ethical issue in humans relates to the potentially easy modification of the germline, whether this involves modification of gametes (reproductive cells) or preimplantation embryos. Limits on this have been set by the WHO, UNESCO, and the Council of Europe. The debate has recently focused on intervention in the germline, as several teams (in China in 2015, then in the United States, and very recently in the United Kingdom) have published findings on the application of the CRISPR-Cas9 system to male gametes or to human embryos, exclusively for research purposes. Recently, an American team used this technique with a view to correcting in the human embryo a mutation responsible for a severe cardiomyopathy[39]. These *in vitro* experiments remained within the confines of the lab, as the embryos were not implanted.

However, the ethical red line of implantation of genetically modified embryos was crossed in November 2018 by a Chinese researcher who, at the Second International Summit on Human Genome Editing in Hong Kong, reported use of the CRISPR-Cas9 technique to modify the genome of zygotes, resulting in the subsequent birth of twin girls with edited genomes. Apart from the fact that the indication for this gene editing seems medically unjustified and likely to result in related diseases[40], this constitutes an intervention in the absence of any disease in embryos the progeny of which will also be modified, and can therefore be likened to a eugenic practice. Moreover, the scientific data reported orally had not been the subject of ethical reflection or of careful review, which is the opposite of what one would expect in terms of research ethics.

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[37] Yamashiro C. et al. (2018). Generation of human oogonia from induced pluripotent stem cells in vitro. *Science*, 362, (6412):356-360

[38] Whatever the current advances in the possibilities of gene editing, the wording of article 16-4 of the French Civil Code allows such an analysis by distinguishing eugenic practices from treatments of genetic diseases.

[39] Ma H. et al. (2017). Correction of a pathogenic mutation in human embryos. *Nature,* 548:413-419

[40] Use of the CRISPR-Cas9 technique to inactivate the *CCR5* gene so as to prevent a possible HIV infection appears illegitimate, given that other techniques are effective. Inactivation, moreover, creates increased susceptibility to other serious viral infections.

Scientific communities unanimously condemned this practice in the current state of knowledge and some debated the need for and scope of a moratorium[41]. However, the organizing committee of the Second International Summit on Human Genome Editing, in parallel with its condemnation of the Chinese researcher's initiative, did not reject the long-term therapeutic possibilities and was in favor of joint reflection on experimental protocols and international regulations without, at any time, mentioning the need for ethical analysis[42]. Moreover, this was a change of position, since at the First International Summit on Human Genome Editing in 2015 the committee had considered genome editing in the human embryo to be irresponsible[43]. Likewise, the Nuffield Council on Bioethics, which was prudent in 2016, states in a 2018 publication that if genome editing were ever to be permitted by law, it should be subject to strict regulation and oversight[44].

These evolving stances also reflect those of other institutions and states. At a 2015 congress organized by the US National Academies of Sciences, Engineering, and Medicine, great prudence in the clinical use of human germline modifications appeared to be the "norm". Two years later, a report by the same National Academies advocated the authorization of human genome editing, including in germ cells, in cases of serious hereditary disease, under strict conditions[45].

In France, while the Parliamentary Mission of the National Assembly in its report of 15 January 2019 highlighted the numerous unknowns that remain in the use of these techniques, the Council of State indicated, in its study of June 2018, that it " *already appears useful to reflect on this perspective, to avoid technical feasibility preempting the required debate on principles*"[46].

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[41] Krimsky S. (2019). Ten ways in which He Jiankui violated ethics. *Nature biotechnology*, 37:19-20
Lander E et al. (2019). Adopt a moratorium on heritable genome editing. Comment in *Nature*, 567:165-168
Daley G et al. (2019). After the storm a responsible path for genome editing. *N Engl J Med.* 380:897-89

[42] National Academies of Sciences, Engineering, and Medicine. 2017. *Human Genome Editing: Science, Ethics, and Governance.* Washington, DC: The National Academies Press

[43] "*It would be irresponsible to proceed with any clinical use of germline editing unless and until the relevant safety and efficacy issues have been resolved, based on appropriate understanding and balancing of risks, potential benefits, and alternatives, and there is broad societal consensus about the appropriateness of the proposed application. Moreover, any clinical use should proceed only under appropriate regulatory oversight. At present, these criteria have not been met for any proposed clinical use: the safety issues have not yet been adequately explored; the cases of most compelling benefit are limited; and many nations have legislative or regulatory bans on germline modification. However, as scientific knowledge advances and societal views evolve, the clinical use of germline editing should be revisited on a regular basis*." First International Summit on Human Genome Editing (2015).
Meyer M. (2018). Irresponsible research? Dis/qualifying the gene editing of human embryos. i3 Working Papers Series, 18-CSI-01.
Rosenbaum L. (2019). The future of gene editing - Toward scientific and social consensus. *N Engl J Med.* 380 (10): 971-975.

[44] Nuffield Council on Bioethics. (2018). Genome editing and human reproduction editing: social and ethical issues, 183 p.

[45] *Human Genome Editing: science, ethics and governance* (2017). Committee on Human Gene Editing: Scientific, Medical and Ethical Considerations. National Academies of Sciences, Engineering, and Medicine.

[46] Révision de la loi de bioéthique : quelles options pour demain ? Council of State study of 28 June 2018.

At the moment, therapeutic intervention in the human genome is banned in France both by article 13 of the Oviedo Convention: "*An intervention seeking to modify the human genome may only be undertaken for preventive, diagnostic or therapeutic purposes and only if its aim is not to introduce any modification in the genome of any descendants*"[47], and by article 16-4 of the Civil Code: "*Without jeopardizing research designed to prevent and treat genetic diseases, no transformation can be made to genetic characteristics with the aim of modifying the person's descendants*".

For the CCNE, great prudence is still called for in therapeutic applications to the human embryo because, apart from the technical uncertainties, the ethical problems associated with transformation of the genome of an individual and subsequently of the human population are a major issue. The principle of an international moratorium before any therapeutic application introducing a genetic modification transmissible to future generations also figures in a recent opinion by the German Ethics Council[48]. Given current understanding, we cannot exclude the possibility of unwanted targets, of mosaic embryos*, or of other complications with unforeseen consequences, in the case of an effect on the epigenome or of an unwanted modification during DNA repair.

New experimental work is required to explore the safety and reproducibility of this approach before envisaging its use in human therapeutics, given that the quality of the manipulation can only be partly checked in the embryo (correction of the gene to be modified, genome sequencing) at preimplantation diagnosis or after implantation, during prenatal diagnosis*.

Lastly, another strategy in genetic repair for therapeutic purposes concerns the replacement of maternal mitochondria. This is practiced outside France by some research teams working on serious and incurable mitochondrial diseases. Even though this concerns mitochondrial and not nuclear DNA, the genetic makeup of the child will include foreign DNA that girls will pass on to their offspring. Even though this mitochondrial DNA is human in origin and has undergone no genetic modification, there are unknowns regarding the long-term evolution of the mitochondrial population[49]. It is essential in this case to consider whether the perspective of treating a child with a potentially lethal disease by introducing functional mitochondria that have not been genetically modified and which are naturally present in human populations constitutes a treatment of disease and not a eugenic practice.

In human populations, when a family presenting a proven risk of the transmission of a severe genetic disease is planning to have a child, the perspective of correction of the genetic makeup of embryos or gametes cannot obscure the eugenic risks of heritable genome editing. This situation necessitates, beyond the scope of the present opinion, specific ethical reflection

[47] Only some European States have signed the convention, which is in force in 29 of them, sometimes with waivers of certain articles and debates on possible changes.
[48] Deutscher Ethikrat (2019). Eingriffe in die menschliche Keimbahn, 280 p.
[49] Kant E. et al. (2016). Mitochondrial replacement in human oocytes carrying pathogenic mitochondrial DNA mutations, *Nature*. 540:270-275.

on the demarcation between healthcare and eugenics. Apart from this major danger, against which legislation in France and in Europe currently provides protection, too many unknowns remain regarding the safety and in part the efficacy of the technique. In contrast, when genome editing is applied not to the embryo, but to human somatic cells, it constitutes therapeutic progress and should be encouraged and developed. In parallel, targeted genome modifications cannot replace the development of prenatal, preimplantation, and preconception diagnosis (cf. the CCNE's reflection on this subject in its Opinions 124 and 129), particularly as with current techniques it is not possible to couple preimplantation diagnosis (made on day 3 of embryonic life) and gene editing (performed on day 0 of embryonic life).

- In the context of somatic gene therapy, human genome modifications constitute medical progress that should be supported. Ethical reflections remain but should be considered like those concerning any gene therapy, because the modifications introduced in the patient are not transmitted to offspring.

- In the context of heritable gene editing, technical and scientific uncertainties regarding the short- and long-term consequences mandate, over and above French legislation, an international moratorium before any implementation. If these technical and scientific uncertainties were to be reduced, there would remain the major ethical question of individual treatment, which however is not aiming to eugenic attempts to transform the human species. Hence, increased genetic knowledge defines, among other things, certain serious and incurable diseases to be related to variations in the individual genome within the human population. Prevention of such diseases from the embryonic stage, by genome repair, calls for particular ethical reflection regarding treatments that may constitute a possible medical procedure in the future.

WHAT IS SCIENTIFICALLY AND ETHICALLY AT STAKE IN THE IMPLEMENTATION OF THESE TECHNIQUES?

Progress made in research, particularly in recent years, holds out the promise of greater understanding of living organisms, human and non-human, without omitting ethical reflection or the putting in place of collective regulations[50]. Basic research should therefore be supported, particularly as gene editing is an extremely effective tool in advancing knowledge. Be that as it may, the scientific community must constantly ask itself about the consequences of the potential use of these applications in humans and in nature, whether this involves the release into the environment of modified organisms with unknown impacts on biodiversity or possible abuses that could raise the specter of the spread of practices that could be qualified as eugenic.

The main problem of these gene editing techniques resides today in the fact that we have no certainty concerning their safety. There is in particular the fear of off-target effects, mosaic embryos, and unwanted modifications of the targeted DNA during its repair[51].

The same applies to the encouragement to develop research aimed at better assessment of the health, environmental, and agronomic risks linked to the targeted use of genetically modified plants, so as to reduce the range of uncertainty regarding the consequences of such use. The domestication of organisms (plants, insects, animals), if it satisfies the needs of humanity, must take into account the humans of today and tomorrow. This prospective vision must be based on multidisciplinary research, as reiterated in the CCNE's Opinion 125, and raises the larger ethical question of risk taking in a context where there is no certainty of efficacy or safety.

Is all germline genome editing unacceptable? Has it not already been done with the aim of alleviating serious and incurable illnesses? There is necessarily a need here for ethical reflection and debate on boundaries so as to avoid eugenic misuse. In 2009, the Council of State wrote the following regarding such misuse[52]: "*eugenics can be defined as all methods and practices aimed at improving the genetic makeup of the human species. It may be the fruit of a policy deliberately implemented by a state and contrary to human dignity. It may also be the collective result of the sum of individual convergent decisions taken by future parents, in a society that promotes the search for the child who is "perfect", or at least free of numerous serious illnesses*."

The application to humankind of gene editing is certainly a source of hope for alleviation of human suffering. However, it can only be applied in healthcare with strict controls and

[50] Liu D. (2018). L'édition du génome est une des grandes révolutions des sciences de la vie https://www.larecherche.fr/biologie-génétique.
[51] An already old publication, though, indicates the possibility of reducing off-target effects one thousand-fold, but few studies use this methodology.
[52] Council of State report in preparation for the revision of the bioethics law (2009).

oversight, above all when it is likely to alter the germline. It is essential to involve not only patients and their advocacy groups and physicians, but also other experts (legal practitioners, ethnologists). One particularity that explains increasing technological interest in medical genetics is the very negative perception for the individual and his or her family and friends, and for unborn children, of serious illnesses and handicaps, most of which we now know to be genetically determined. Steven Pinker considers that whatever is technically possible in reducing the burden of disease can and should be used[53].

This argument raises two distinct ethical questions: the possible creation of unrealistic individual or societal expectations, as not all diseases stem from identified genetic perturbations; and the choice to be made between individual benefit (eliminate the disease/handicap) and collective risk (risk of social transgression, refusal of "differences"). On what ethical basis, for instance, can a choice be made between the practice of selecting embryos free of a disease-causing mutation at preimplantation diagnosis and the possibility of correcting this mutation by gene editing in affected embryos to prevent, after reimplantation of the treated embryo, the onset of the disease in the unborn child?

With this in mind, would it be acceptable to repair the human genome, including in germ cells, to prevent the occurrence of a serious hereditary disease for which preimplantation diagnosis is ineffective when all the embryos are affected (both parents have a frequent, autosomal recessive disease*, such as cystic fibrosis)? This is an exceptional circumstance, but its frequency will very likely increase given medical progress.

In parallel, the problem is posed from the angle of the conception of a "healthy child" and of to what extent such a wish, in families that carry hereditary diseases, is akin to a request for assisted reproductive technology, which may generate tension between specific wishes regarding the child and global health policies.

A distinction should also be drawn between proven monogenic diseases (accessible to preimplantation or prenatal diagnosis) and possible, but uncertain, diseases associated with a genetic variant, a susceptibility gene[54], or simple variants associated with certain morphological characteristics, such as small stature, which sometimes are experienced as real handicaps. Ethically also, the lack of consent of the unborn child raises a question: how will the child experience this modification and what is the parental responsibility? Is there not a risk of "grievance" on the part of the child who is born "modified"?

Reflection does not obviate the need for analysis of the risks of genetic standardization: what sense would there be in a world where differences, handicaps for example, or even one or other characteristic, would be "unwelcome"? What drawbacks could arise from creating

[53] Pinker S. (2015). The moral imperative for bioethics. *Boston Globe* (01.08.2015).

[54] Some argue for inactivation of susceptibility genes, for example the homozygous ApoE4 genotype associated with the development of Alzheimer's disease, or the mutation of the *PCSK9* gene associated with familial hypercholesterolemia. The limits of such an approach are blurred and misuse is possible.

irreversible biases in human evolution according to standards established in the name of principles held by some people?

In the present context we should not downplay the development of a form of eugenics based not only on refusal of handicaps and of differences, but also on the individual or societal prospect of enhanced capacities attractive to proponents of transhumanism* because they constitute a sort of emancipation of human nature.

However, correction at the embryonic stage of a mutated gene that inevitably at birth or in the early years of life results in suffering, both physical and mental, even death, seems to involve care, not eugenics. This purely therapeutic approach, if authorized, would require extremely strict oversight, like that applied to preimplantation and prenatal diagnoses, as reiterated by the CCNE in its Opinion 107.

Other genome engineering and synthetic biology* techniques are not limited to "correcting" genetic modifications associated with serious and incurable diseases, but also seek to reprogram the genome so as to give it properties it does not naturally have. Here is an example: the primary function of the enzyme Cas9 is to cut a DNA sequence, but it can also intervene in control of the epigenome. A precise part of the epigenome can therefore be targeted to localize genes and to convey effectors able to activate or switch off the expression of selected genes, without altering their sequence. "Interrupters" can be added to induce these epigenetic modifications by light (optogenetics), for instance, or by any other easily manipulated signal. This approach seems like an innovative therapeutic approach to certain neurological diseases, but raises the possibility of someone altering for specific purposes the expression of genes and hence the behavior of an individual or even a population.

These advances also call for the provision to society of wide-ranging information on current knowledge of the genome and for ethical debate on the health risks raised by genome editing and on the tensions that may arise between the wishes of some and a loss of global solidarity following the spread of these technologies. What results from scientific discoveries is a matter of collective responsibility, and scientists too are citizens, even though their scientific and technical knowledge confers on them a special responsibility, that of informing society of their advances and doubts[55].

Advances in genome editing techniques and the ease of implementation of some of them, as recently with the CRISPR-Cas9 technique, are likely to generate tension between individual aspirations and collective solidarity. The accompanying questions parallel those posed in other areas of human health by the development of personalized and costly medical techniques. The scope of these questions is international, extending beyond the definition of national standards and paralleling the essential and continuous provision of information to everyone on the advances and potential risks.

[55] CCNE, Opinion 109: Society and the communication of scientific and medical information: ethical issues (2010).

Rules regarding responsibility, governance, risk management, and public decision making in situations of scientific uncertainty are essential for the understanding and acquisition of increasingly complex knowledge. The scientific community has a special responsibility in society's acceptance of innovative processes, should pay careful attention to the reflections overseen by the WHO[56], and should help set up international scientific bodies such as ARRIGE[57] and take part in the deliberations at events like the International Summits on Human Genome Editing. Apart from the responsibility of the scientific community, society as a whole should take part in the debate and define the world that it would be desirable to pass on to future generations.

Endorsement of the idea that everything could be regulated by means of a tool of governance or dialogue would assume that the technique is neutral with respect to its object and would negate reflection on its values, the range of which should be developed as widely as possible[58]. In the first instance this is a cultural problem, a choice of civilization for our societies, if culture is considered as the framework for reflection within which humanity and each one of us evolves. Thus, Hans Jonas calls for caution and vigilance in the face of utopian misuse of techniques, and for responsibility. The scientific community should be ever vigilant regarding the use of these techniques in humans and the natural world and their potential consequences, such as dissemination of genetically modified organisms with unknown impacts on biodiversity or perverse applications raising fears that eugenic practices will become commonplace.

In terms of codes of conduct, the scientific and medical communities must also be alert to conflicts of interest that may reduce their credibility in the eyes of society and risk hampering the development of research. Such conflicts of interest between researchers and commercial businesses arise too often, even within scientific institutions[59], including in the field of human gene editing, because of the potential for financial gain.

Scientific work on genome engineering has raised fears associated with the great myths of the creation of living beings (Frankenstein, golems...) that feed fears of the "mad scientist". Those who fuel these fears are guilty of defying society by depicting scientists as irresponsible and prey to obscure motivations, and not as fully fledged citizens. The CCNE forcefully rejects

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[56] Reardon S. (2019). World Health Organization panel weighs in on CRISPR-babies debate. *Nature,* 567: 444-445.

[57] Association for Responsible Research and Innovation in Genome Editing, the creation of which was promoted by INSERM.

[58] Devictor V, Bensaude-Vincent B. (2016). From ecological records to big data: the invention of global biodiversity. *Hist Philos Life Sci.* 38(4):13. doi: 10.1007/s40656-016-0113-2.

[59] Krimsky S. & T. Schwab. (2017). Conflicts of interest among committee members in the National Academies' genetically engineered crop study. *PLOS.* https://doi.org/10.1371/journal.pone.0172317
Guillemaud T. et al. (2016). Conflicts of Interest in GM *Bt* Crop Efficacy and Durability Studies. *PLOS.* https://doi.org/10.1371/journal.pone.0167777
Strom S. (2016). U.S. panel under fire for its ties to biotech. *The New York Times*. 28 December 2016.

such unproven assertions and considers that the role of researchers in the acquisition of knowledge is indispensable to the progress of society and should be respected and valued.

For its part, the scientific community, its members and institutions, should show humility by acknowledging its ignorance of the sometimes unpredictable repercussions of new techniques. Even though international competition is great and funding sometimes promotes applied research, researchers should know how to articulate the doubts and questions raised by the applications of their work. Scientific evaluation must take into account ethical problems through careful and continuous monitoring of research projects. Such monitoring will only be effective if its scope transcends the national perspective to become international. It is essential to raise awareness among young researchers and students of the ethical issues in play by offering them suitable instruction.

Finally, scientific personnel and institutions face the major ethical challenge of sharing scientific knowledge, without omitting reflections on its applications and on the limits to be imposed on research, not only with society as a whole, but also with political decision makers.

CONCLUSIONS AND PERSPECTIVES

Genome engineering has for decades been a major tool in the growth of knowledge. Its value in research, including in the human embryo, is unquestionable. But its applications to all living organisms is subject to debate and questioning. What ethical answers can be brought to bear on this technological progress? Although there are still many unknowns, it is nonetheless necessary to develop research, both theoretical and applied, and to apply ethical principles to it[60]. From this point of view, the ethical debate too often lags behind technological advances and so becomes hard to guide effectively.

In the framework of necessary systemic research and evaluation of biotechnologies developed in a context of scientific uncertainty, it is indispensable to underscore the various levels of responsibility of researchers and institutions working in these fields and to develop an in-depth dialogue within society about what is at stake and the technological choices to be made or postponed.

Gene editing is one of the tools in development for future biological and medical research. It is closely linked to synthetic biology and to the development of organoids from pluripotent stem cells, synthetic gametes, and human organs in animal chimeras. CRISPR-Cas9 technology is emblematic of emerging techniques whose targets are universal and likely to modify deeply, even globally, certain human behaviors, and our environment. Apart from major ethical issues raised by modification of the human germline and the implications for ecosystems, several corollary questions should be emphasized.

- The dissemination of this new technology (CRISPR-Cas9) and the prospect of future genome modifications are likely to generate unrealistic social expectations that cannot be met, because of our lack of knowledge of the methodologies used, because of our still imperfect understanding of the genome and epigenetics, because of the unpredictability of natural evolutionary processes, and also because this technology cannot be offered to everyone, thereby increasing the risk of a medical science that exacerbates social inequalities.

- As the use of CRISPR-Cas9 technology for therapeutic purposes in the human embryo is banned in France, but authorized elsewhere, the problem of "medical tourism" arises, as in other medical fields, and must be taken into account in international agreements that complete national policies. This problem is all the greater because use of CRISPR-Cas9 by "do-it-yourself" biologists outside all ethical and regulatory constraints cannot be excluded.

- More broadly, genome editing could be diverted from all health objectives and used to develop formidable weapons (resistant bacteria or viruses, epigenetic perturbations of individuals and populations). The French parliamentary office for evaluating scientific and

[60] Nuffield Council on Bioethics (2016). Genome editing, an ethical review, 128 p.

technological choices (OPECST) in its report of 9 February 2017 raised the question of potentially malicious uses and underlined the role of researchers in research that is responsible, notably in terms of biosecurity.

In view of these difficulties and risks, it behooves us to emphasize the ethical responsibility of researchers and of scientific institutions in terms of the transfer of research findings to biotechnological applications. Also, the legal and regulatory frameworks stemming, for example, from bioethics laws and the Oviedo Convention, must be permanently spelled out and specified in the professional circles concerned.

The debate on the use of gene editing tools necessitates the continuous association of supervised development of basic research and reflective sharing of knowledge. Rigorous information for society as a whole is required to avoid inappropriate reactions through lack of awareness of the benefits, unknowns, and inherent risks of emerging new biotechnologies.

Beyond this information, individual and social choices do not obviate the need for a debate that considers the scientific information placed within the global context of the variability and evolution of living organisms as well as humanist perspectives of sustainable and shared development. The issues to consider also concern existing legal and regulatory aspects, human health[61], and the living world regarding the genome editing of organisms[62]. In health and biodiversity, the CCNE considers that, while supervising with relevance and rigor the research applied to living organisms and medical interventions in humans, notably in the embryo, there should be clearer promotion of the development of knowledge in basic research in the life sciences, particularly in the human sciences.

Principles proposed and perspectives

Given the difficulties and risks inherent today in the use of gene editing, but also the hopes that it raises, the ethical responsibility of researchers and scientific institutions in transfer of research findings to biotechnological applications should be underscored, and the legal and regulatory framework stemming from, for instance, bioethics laws and the Oviedo Convention, should be permanently spelled out and specified in the professional circles concerned. Hope and vigilance therefore constitute principles in tension with each other.

[61] While the French Civil Code proscribes eugenics "without jeopardizing research aimed at the prevention and treatment of genetic diseases" (article 16.4), the French Health Code considers that research and intervention should be examined and promoted in accord with advances in knowledge, as in the use of induced pluripotent stem cells or gene editing (including the perspectives in terms of xenografts).

[62] The difficulty of tracking some genetic changes and the prospect of the massive extermination of species mandate examination of the relevance of existing legislative and regulatory safeguards regarding genetically modified organisms, in terms of protection of health and of the environment, and exclusion of all scientific and normative value from the concept of New Plant Breeding Techniques, given the diversity of methods considered.

Sheila Jasanoff, a professor at Harvard University, also calls for awareness among all citizens, considering that experts *"assert that the public should be educated by experts before any informed dialogue can take place. But the problem is not only a lack of technical knowledge. The answer to how we should act does not reside in technological details. It is our responsibility to decide, as parents and citizens, whether our present genetic preferences should be modified forever in our children and in their children."*

This injunction should also be extended to the living world, taking into account our choices in terms of a living space for all of humankind.

1. Laboratories doing basic research involving the new techniques of gene editing should be encouraged. Whatever the relative ease of their implementation, it is important to develop experimental approaches to make these techniques safer, even reversible, and to regulate their application to living organisms.

2. The applications of gene editing to non-human living organisms are an undeniable source of potential benefits. However, thought should be given to animal welfare and to possible uncontrollable, even dire consequences, like disruption of ecosystems and evolutionary systems. For example, in the control of vector-borne diseases, genome editing, especially when associated with gene drive, may well have the opposite of the desired effect: the emergence of new potentially more dangerous disease vectors. The organisms concerned should only be released from laboratories after systematic and meticulous evaluation of the potential risks, and even following implementation of measures enabling reversibility and continuous monitoring. It also seems essential to consider plants, fungi, and animals with edited genomes as genetically modified organisms.

3. In somatic gene therapies, human gene editing constitutes medical progress and should be supported. Ethical reflections remain but, because modifications introduced in the patient are not passed on to the next generation, such treatments should be considered like any other gene therapy.

4. Because of the extent of the technical and scientific uncertainties associated with the short- and long-term effects of modifications to the human genome that are passed to future generations, above and beyond French legislation an international moratorium should be imposed before any implementation. These technical and scientific uncertainties, even if reduced, would remain the main ethical question of an individual treatment that is not part of a eugenic attempt to transform the human species.

So, advances in genetic knowledge enable, among other things, the correlation of certain serious and incurable diseases with variations in individual genomes within the human population. The prevention of such diseases at the embryonic stage by genome repair calls for particular ethical reflection regarding care that could become a medical procedure in the future.

APPENDICES

Appendix 1: Members of the working group

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Margaret BUCKINGHAM (until October 2016)
Hervé CHNEIWEISS (until April 2018)
Laure COULOMBEL
Pierre-Henri DUÉE
Anne DURANDY–TORRE (rapporteur)
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Patrick GAUDRAY (until October 2016)
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Michel VAN PRAET (rapporteur)
Alice RENE (until April 2018)
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Appendix 2: Experts consulted

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Yann LE CAM, EURORDIS (European Organisation for Rare Diseases)
Morgan MEYER, Centre de Sociologie de l'Innovation, Ecole des Mines de Paris (Mines ParisTech)
Grégory KATZ, Chaire ESSEC Innovation Thérapeutique et Institut d'Économie et Management de la Santé à l'ESSEC Business School (Paris-Singapore)
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Alta CHARO, Professor of Law and Bioethics (University of Wisconsin–Madison, USA)
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Appendix 3: Glossary

Autosomal recessive disease: Hereditary disease due to two mutations, one carried by the maternal allele and the other by the paternal allele. If a single mutated allele from one or other parent is enough to result in a disease, it is called an autosomal dominant disease.

CRISPR-Cas9: This gene editing technique uses an endonuclease (Cas9) that recognizes and cuts certain DNA motifs called CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats).

DNA: Molecule comprising an assembly of four nucleotides: adenosine (A), thymidine (T), cytosine (C), guanosine (G).

Epigenome: The epigenome (set of proteins and enzymes) is responsible for the regulation of the expression of genes, by biochemical modifications (methylation, among others) of DNA, or of chromatin, thus allowing, or not, factors to access the gene thereby enabling its transcription into RNA, and then protein. Small RNA regulators are also involved in this regulation. Epigenetic variations occur without changes in the gene sequence and are reversible.

Eugenics: The term eugenics, coined by Francis Galton in the 19th century, corresponded at the time to a conservative movement of evolutionary thought that advocated the application of selection to humanity. Today, it covers a set of methods and practices designed to improve the genetic heritage of the human species. It may result from a political decision of a state and lead, for example, to a refusal of immigration, segregation and control of marriages, or the forced sterilization of certain populations. It may also result from the individual stances of parents or doctors regarding refusal of handicaps that may extend to a wish for the "perfect child". The repair of a genetic alteration is not a eugenic practice but, between the refusal of certain diseases and the promotion of racist concepts, the term eugenics can be used in different perspectives that should be specified and enriched by ethical reflection, particularly as new gene editing technologies are likely to fuel a range of tendencies, and even social demands.

Gene: Segment of DNA transcribed into RNA and then translated into protein. The human genome contains approximately 25 000 genes. Each individual inherits two copies or alleles (one paternal, one maternal) of each gene.

Gene drive: Use of CRISPR-Cas9 technology to enable the very fast transmission of a gene in a population of animals that reproduce sexually (mosquitoes, for instance).

Gene therapy: In human medicine, gene therapy consists of the introduction of a healthy gene in an individual with a genetic disease. The healthy gene is inserted in a viral vector, transferred in vitro into somatic cells (hematopoietic cells) or in vivo in a tissue (muscle, for

example) so as to correct the genetic disease. The gene is inserted randomly into the recipient's genome, a drawback that ongoing clinical trials are trying to mitigate. Gene therapy is currently applied to somatic cells only (not germ cells).

Genome: The genetic material encoded in DNA. It contains coding DNA sequences (exome), which are translated into proteins, and noncoding sequences.

Genome engineering (gene editing): These new techniques use endonucleases to cut a gene very precisely, either to inactivate it or to replace it with a functional gene. This extreme precision is made possible by the use of a guide RNA prepared by the experimenter to aim the endonuclease at the chosen DNA sequence. This technique can be applied to somatic cells to enhance the performance of gene therapy. It can also be applied to zygotes or gametes, thereby modifying the germ cells such that these changes are transmitted to future generations. The law currently prohibits this in humans and applies various restrictions to its use in other living organisms (genetically modified organisms). Several methods are used, including the technique called CRISPR-Cas9, which is currently the most developed.

Induced pluripotent stem cells: These pluripotent stem cells, produced in the laboratory from somatic cells (skin fibroblasts, for example) acquire the potential to differentiate into any cell of the body, including precursors of gametes. The distinction between somatic and germ cells in vertebrates, including humans, is thus questioned by the totipotency of induced pluripotent stem cells.

Mosaic embryo: Embryo in which only some cells have been modified by gene editing.

Mutagenesis: Introduction of mutations in a DNA sequence by the action of chemical or physical agents. It may be random or directed when it targets a particular sequence.

Mutation: Variation of a gene (point mutation: change of a nucleotide base, but also the deletion or insertion of one or more bases). When the mutation does not alter the synthesis of the amino acid, it is called "silent". When it does change the amino acid synthesized, it may have no effect (polymorphism) or cause a disease.

Prenatal diagnosis: Diagnosis made by genetic examination of trophoblast cells of a fetus (at about 12 weeks) at risk for an incurable (in the current state of knowledge) genetic disease or a chromosomal aberration. **Preimplantation diagnosis** consists in studying the genome of one or two cells of a human embryo obtained after in vitro fertilization, before its implantation.

RNA: Molecule comprising an assembly of four nucleotides: adenosine (A), thymidine (T), cytosine (C), uracil (U). It results from the transcription of DNA and allows the translation in amino acids and then proteins. A codon, which comprises three nucleotides, codes for one amino acid.

Somatic cells: In an adult organism, somatic cells correspond to all cells except for the **germ cells**, which give rise to gametes (oocytes and spermatozoa).

Synthetic biology: Scientific and biotechnological discipline that involves the design of new organisms or artificial cells in the laboratory. Synthetic biology combines biology and the principles of engineering so as to design, as in electronics, biochemical circuits using standardized and interchangeable components. Biochemical circuits can then be combined and integrated in tissues or living cells.

Transgenesis: Deliberate introduction of one or more exogenous genes into the genome of a living organism.

Transhumanism: Cultural and intellectual movement advocating the use of science and technology to improve the physical and mental characteristics of human beings (human enhancement project). It considers handicaps, diseases, and aging as unacceptable. This doctrine, whose premises are old, was dubbed transhumanism in 1957 (by Julian Huxley) in a context where the term eugenics was universally condemned.

Zygote: A cell formed by the fertilization of an egg by a sperm in animals including humans.

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