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Ethical and social perspectives on the use of gene editing in humans

Short report based on the report "Overview of ethical and social issues of human gene editing as raised by policy documents"
Howard and Niemiec (2019)

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I- INTRODUCTION

This short report provides a summary of different ethical and socials aspects relevant to the consideration of using gene editing approaches (with tools such as CRISPR-Cas9) in humans. The focus of this summary is on hereditary germ line gene editing and its proposed use in the clinic. We, however, also briefly mention uses in research as well as in somatic cells. For more information on ethical and social aspects of gene editing as well as for a full list of references, we refer readers to the longer report "Overview of ethical and social issues of human gene editing as raised by policy documents" Howard and Niemiec (2019). Finally this report does not address the specifics of mitochondrial replacement; however, some of the ethical and social aspects do overlap.

II- MAIN "META" QUESTIONS TO CONSIDER

The overall "meta" questions one may consider for the context of using human germ line gene editing in humans is similar to that for many other new tools or approaches. For example, stakeholders may want to ask:

How do the (potential) benefits of using this new tool or approach weigh up to the (potential) risks and harms?

This approach is clearly consequentialist in nature, and other questions stakeholders may consider include whether or not there are any deontological reasons for or against using a certain tool or approach. For example, stakeholders' stance on the status of the embryo, may dictate whether or not they agree with the use of embryos in research. For the purposes of this short report, we present a summary of ethical, and social issues under the heading of potential concerns without providing full arguments (or their origins).

Regarding the weighing up of (potential) benefits and harms/concerns (or "calculation" of the cost-benefit ratio), this approach is often complicated by at least three aspects: a) the scope of benefit and harms is very large and goes beyond medical or physical aspects; b)the evaluation is often value-laden; b) there is a large number of uncertainties surrounding benefits and harms.

a) Scope of benefits, risks/harms goes beyond (individual) physical or medical aspects

It is important to recognise that benefits, risks and harms have a very broad scope and need to be considered beyond the (individual) physical or medical realm. For example, benefits could be financial for a specific population or stakeholder group. Harms may be societal, for example in the form of injustices between individuals or countries; this can include problems with unequal access and discrimination.

b) Value-laden evaluation

The answers to benefit-harm evaluations are often value-laden. That is to say that the importance placed on different values or outcomes may lead to different perceptions of what is an important risk or benefit and may lead to different views on the risk/benefit calculation by different stakeholders. It is important in this

case to attempt to be as explicit as possible about different stakeholders' (potentially implicit) values, a priori beliefs, agendas, and/or prioritization of outcomes. For example, some stakeholder groups may prioritise the value of innovation or economic development over the precautionary approach [2] or concerns over negative social impacts.

c) Uncertainties surrounding new technologies

The fact that technologies and/or approaches are novel means that there is a lack of concrete evidence regarding many scientific aspects as well as social or legal impacts. Attempting to anticipate risks and benefits without such evidence makes the evaluation of novel technologies and approaches particularly sensitive. The discussion regarding the use of gene editing in humans, especially the use of germ line gene editing in humans is currently shrouded in uncertainties regarding many aspects (See below).

III- SOMATIC GENE EDITING IN THE CLINIC

What is Somatic Gene Editing (SGE)?

Somatic cell gene editing (SGE) in humans involves the modification of DNA in somatic cells; theoretically, these modifications should not be passed on to offspring. The main reason proposed to use somatic gene editing in humans in the clinic are to cure or treat persons already living with a disorder. Examples of diseases for which somatic gene therapy is currently being researched include, HIV, Sickle Cell Disease, and different forms of cancer (Clinicaltrials.gov; tinyurl.com/yyex5s8g). For many reasons, SGE is considered to be in the same category as more traditional gene therapy and as such, is considered to elicit less complex and weighty ethical, legal and social issues than germ line gene editing. For example, many authors believe that the current legal frameworks around gene therapy can be appropriately applied to somatic gene editing.

What are the ethical and social issues salient to SGE?

If we consider SGE with tools like CRISPR-Cas9 as a new way of conducting gene therapy, we may consider the following ethical, social and regulatory aspects, many of which overlap with germ line gene editing: safety; acceptable (therapeutic and/or enhancement) uses; protection of vulnerable persons (patients and families); the informed consent process; investment (research and development) approaches; justice in access to therapies/treatments; responsible public engagement: and oversight of clinical trials and regulatory issues. Since this summary has as a goal to focus on germ line gene editing, we only provide a very brief overview of some aspects as examples.

Safety

The challenges or concerns surrounding SGE include safety of the gene editing procedure (e.g. off-target events, side-effects from the process of inserting the gene editing machinery) and what the consequences may be on humans

[2] https://www.europarl.europa.eu/thinktank/en/document.html?reference=EPRS_IDA%282015%29573876

physically. Importantly, clinical trials are currently on-going (Clinicaltrials.gov; tinyurl.com/yyex5s8g)) and it appears that physical safety to participants is not an obvious problem to date.

Uses: which therapeutic uses will be deemed acceptable and will potential "enhancement" uses be addressed?

Additional concerns include what diseases or conditions would be eligible for SGE; in particular, it is uncertain how the line between disease treatment or cure will be delineated from enhancement (e.g. using SGE to enhance a currently "normal" or non-diseased trait). Issues surrounding the different definitions and concepts of "enhancement", "disease" and "normal" complicate this debate. Notwithstanding, while many stakeholders appear to support the use of SGE for therapeutic reasons, they also appear to discourage the use of SGE for enhancement purposes. Aspects that fuel this "anti-enhancement" stance include among others, issues of social justice (e.g. would this be accessible to all? Would it provide unfair advantages to some?) of responsible prioritisation, and potentially negative impacts in society (e.g. discrimination, eugenic tendencies).

Justice

Furthermore the potentially high cost of the procedure raises questions such as who will pay for the procedure if offered (regularly) to patients in the clinical context and if the procedure will be equally accessible to different populations (within a country as well as across continents) or only to the rich (countries and/or individuals)? While these questions are not specific to SGE (e.g. many new technologies in genetics and health care in general raise this question) they remain, nonetheless, important ethical and social issue that must be addressed along side attention to more scientific and technical matters. This report however, is focused on germ line gene editing, hence this section on SGE is kept brief and we refer readers to the longer report prepared for the committee for further information[3] on SGE.

IV- GERM LINE GENE EDITING

What is germ line gene editing (GLGE)?

Germ line gene editing (GLGE) in humans or hereditary germ line gene editing involves the modification of DNA in cells that will ultimately be passed on to offspring and hence the modifications should be inherited by future generations.

GLGE in the research context

The use of GLGE in the research context (i.e. where research embryos can not be used to establish a pregnancy, and in many countries can not be allowed to grow past 14 days) is currently underway in a number of different countries worldwide (e.g. USA, Sweden, China, UK). GLGE in the research context can be performed with different goals in mind; for example, i) to study processes and phenomena such as embryogenesis or (in)fertility; to refine and improve the tools used; and to study

[3] "Overview of ethical and social issues of human gene editing as raised by policy documents" Howard and Niemiec (2019)

how gene editing tools can be used to "correct" disease alleles in humans. Each different context, brings with it different specific ELSI as well as more common ones (e.g. the use of embryos in research, informed consent of gamete or embryo donors). Research on correcting disease alleles is distinctive, however, in that it's end goal (i.e. to see if this tool can be used in the clinic to establish a pregnancy) is, itself controversial. Since we focus herein on the proposed use of GLGE in the clinic, we only briefly overview some potential benefits and ethical and social concerns of the research context.

What are potential benefits of GLGE in the research context?

Furthering Science

The use of GLGE in research can allow researchers to study and better understand processes such as embryogenesis and phenomena such as infertility as well as refine the tools used. Some research is also being conducted with the goal to use gene editing to correct disease alleles in humans.

Support for scientific freedom and economic development

Allowing researchers to pursue research on GLGE could also be considered a way to allow for science to progress and as a promotion of scientific innovation. Such use may also allow for the development of products and services that could allow certain stakeholders to benefit economically.

What are ethical and social concerns regarding the use of GLGE in the research context?

Use of embryos

Currently GLGE is being used in embryos (or in germ line cells to make embryos) in the research context only. Due to widespread legislation, such edited embryos can only be left to develop for 14 days, after which they must be destroyed. The use of embryos in research (even without GLGE) is a contentious issue in its own right and different legislation exists to regulate the use of embryo in research (including whether embryos can be created for the sole purpose of being used in research as opposed to using "surplus" embryos no longer needed for IVF).

The use of embryos in research can be seen as problematic for many reasons; due to space limitations we only address a few here, please refer to the longer report for additional information. For example, how one understands the moral status of the embryo (e.g. as being the same as living persons, as having no moral status, or intermediary to these 2 extreme stances) would imply different levels of protection for the embryo. For example those who believe that embryos have the same moral status as living persons would not agree with the use of embryos in research that leads to the destruction of embryos (regardless of the context of GLGE).[4]

Specifically regarding the use of embryos in research for GLGE, and in particular with the goal of refining the technique so that GLGE could be used in the clinic, the use of embryos may be particularly problematic due to the potentially high

[4] Overview of ethical and social issues of human gene editing as raised by policy documents" Howard and Niemiec (2019)

number of embryos needed and the undue burden this may place on women to donate eggs(Niemiec & Howard, 2020). Given that in some countries, egg donors may be financially compensated in the range of 5000 Euros, there is also concern about undue inducement to participate in research, especially for vulnerable women.

Informed Consent

GLGE research performed for refinement of the tools for ultimate use in humans and involving gamete donors may also raise concerns surrounding informed consent. In particular, there are concerns regarding the poor readability of the forms as well as whether donors are properly informed about the sensitive nature of the research and that at least a portion of their genome will be sequenced(Niemiec & Howard, 2020). The latter then raises much of the ELSI about genomic sequencing in research including aspects related to storage, secondary uses, and return of results, as well as aspects about privacy and confidentiality of the genomic data(Niemiec & Howard, 2020).

GLGE in the clinical context

The proposed use of this type of DNA modification in the clinical context raises a large number of ethical, legal, and social implications (ELSI), not least because the heritable alteration of the human genome (i.e. to establish a human pregnancy resulting in a live birth) is currently illegal in most Western countries (including all European member states via binding instruments such as the clinical trials regulation[5] as well as national legislation(Boggio, Romano et al., 2020)). This said, there are prominent scientists who argue there are compelling reasons to pursue GLGE (Church, 2017) and other prominent scientists who are calling for a global moratorium on clinical uses of human germline editing (Lander, Baylis et al., 2019).

What are potential benefits of GLGE in the clinic?

GLGE as a curative or preventive treatment

Potential benefits of using GLGE in the clinic have been suggested relating to the curing, treatment and/or prevention of disease. In particular, proponents have suggested that for some couples with genetic disease, GLGE may be the only way couples could conceive of a genetically related child without passing on a genetic disease. This stance has been questioned, among others, due to existing alternative approaches that could help parents not pass on disease alleles to their children (e.g. pre-implantation genetic diagnosis; see below). Some authors have also suggested a population-wide benefit related to reducing the number of genetic diseases in a population.

Support for Reproductive Autonomy of Parents

Other stakeholders have identified one of the main benefits of GLGE as supporting the reproductive autonomy of parents who want a biologically related child with a specific trait (e.g. not having disease X) (Bioethics, 2018). As discussed by many authors, including the Nuffield Council on Bioethics, the use of the notions of

[5] Clinical trials - Regulation EU No 536/2014; https://ec.europa.eu/health/human-use/clinical-trials/regulation_en

'treatment" or "curing" may not be congruent with how these terms are usually used in health care (Bioethics, 2018). The argument is based on the fact that before the use of GLGE there is no person born that would need treatment per se. In fact GLGE would be performed on germline cells or embryos and so one would be preventing a person from being born with a specific disease, but not curing or treating a person per se(Baylis, 2019). This demarcation is relevant when considering the "need" for GLGE in society (see below).

What are potential risks and concerns regarding the use of GLGE in the clinic?

Many of the ELSI surrounding GLGE are not new per se; many are similar to the ELSI raised by other reproductive technologies such as in vitro fertilization and PGD. Other ELSI, especially those related to the more obvious generational effects are considered specific to GLGE.

Uncertainty regarding safety and physical harm

A large area of uncertainty pertains to the scientific safety of GLGE and what the physical side-effects may be for individuals in whom such processes are performed. Uncertainties still remain about factors such as off-target events and mosaicism; unknown or not completely understood pleiotropy of genes may also be negatively affected by editing. (Please see the scientific report for more information). That said, there appears to be a consensus from a large number of stakeholders, including genetic experts that the science is not ready to be used for GLGE in humans. This stance is at the heart of the calls for a moratorium of the use of GLGE in humans in the clinic (Lander et al., 2019). Importantly, physical risks and side-effects will need to be monitored for some time.

Concerns about first in human trials, support for autonomy and informed consent

In essence the first person(s) born with GLGE may, in essence, be living a life-long clinical trial including regular monitoring. This may also be the case for their children and grandchildren, hence a multi-generational clinical trial. Some authors have mentioned that parents should not have the right to provide consent for their children to live such important and invasive impositions. It has been suggested that we do not, currently have the, logistical, regulatory or ELSI frameworks to support a responsible approach to such life-long, multigenerational monitoring.

From the parents' perspective, allowing for GLGE to fulfil the parents' wish for a biologically related child without a specific disease would support their reproductive autonomy. That said, the issue of consent may still be unclear as it is not assured that the complete list of risks and unknowns of the GLGE procedure for reproductive means could be properly explained to couples (especially initially when experts themselves are likely to be uncertain). This is often the case for new treatments but these are usually used to treat an already existing person so the chance to fulfil the medical need may outweigh all the unknowns; however, this is not the case for reproductive GLGE (where there is no person before GLGE is applied and there is no medical need per se). While the Nuffield Council for Bioethics has stated that supporting such a wish would be valuable, other authors have argued that the state has no duty to support a couple's wish for a biologically

related child (and parents have no right to this) (Denier, 2006) so the importance of supporting parental reproductive autonomy is not clear.

From the future child's point of view, (and his/her own future children) clearly no consent is obtained as this is simply impossible. Authors have pointed out that no future child is ever asked if they want to be born either and that parents regularly make all the important (medical) decisions for children until they reach an appropriate age to make their own decisions. That said, GLGE and it's potential implications and risks for individuals and societies (in the future) may be so invasive and important that such a decision can not be left unilaterally to individual couples to decide.

Human genetic diversity

Another potential level of risk may involve the genetic diversity of humans in the long run. The question here is whether the regular removal of certain alleles in the population may affect the range of genetic diversity (i.e. reducing it) and potentially rendering the population less fit (in a Darwinian sense) to withstand changing environments. Such risk would likely only be seen after many centuries or more, and remains highly speculative. This type of risk is mentioned here nonetheless to show the magnitude of range of different uncertainties that germ line gene editing raises around safety and risk for individuals, societies and human species as a whole.

Questioning the "Need" for GLGE?

Some authors have questioned whether there is a "true" need for GLGE. This question about need is based primarily on two aspects: 1) there already exists a technique called pre-implantation genetic diagnostics (PGD) which can identify embryos with(out) disease-alleles and this technique is currently offered to parents who carry disease alleles and wish to have a child without such alleles. PGD has been used for over a quarter century and the risks are well known. 2) It has been calculated that there is likely to be a very small number of couples who would not be able to use PGD for biological reasons(iotti M, 2019) and for whom GLGE would be the only way to have a genetically related child without a given disease.

Some stakeholders have also suggested that instead of using GLGE to have a disease-free child who is also genetically related to the parents, somatic gene editing may also, in some cases, be conducted in utero or as soon as the child is born in order to treat or cure the baby as early as possible. This would then keep the procedure on the individual level.

Justice

The issues of justice and equitable access to new technologies are not specific to GLGE but they are certainly very pertinent given the potentially high costs of developing GLGE (in research) and offering GLGE in the clinic. Moreover, it is important to highlight that simply because previous technologies may not be fairly distributed or accessible to all, this is not a good reason to conclude that such injustices would be acceptable for gene editing. Specific question salient to this issue and previous concerns above include: Does it make sense to be contributing

so many financial and human resources to developing a technology and approach that has a questionable medical need?

Negative Impact on Society

Related to many of the issues already described above, there may also be negative impacts on society as a whole. For example, if only the rich could afford GLGE then would two different genetic classes result: groups who are devoid of specific disease (alleles) and those who still have to manage diseases? Could there be different acceptability or discrimination of these groups in society? Could acceptability of those with disabilities decrease if there is a societal expectation that parents should try to have children without specific diseases? Would parents experience undue pressure to used GLGE to avoid certain phenotypes in their children? Could these issues point to a potential increase in eugenic-based mentality (including liberal eugenics)?

Protecting human dignity

There is a concern that GLGE may challenge the notion of human dignity. Both the Oviedo convention[6] and the UNESCO Universal Declaration on the Human Genome and Human Rights[7] refer to the respect or protection of human dignity in the context of the human genome. While the notion of human dignity is not easily boiled down to a few sentences, Segers and Mertes (2019) (seggers & Mertes, 2019) provide a helpful discussion on the concept of human dignity in the context of GLGE and its relationship with concepts already discussed in this document, including eugenics, the idea of common heritage, the principle of equal birth as well as justice.

Acceptable Conditions for use of GLGE

Problematic issues are raised regarding which conditions would be eligible for GLGE applications in the clinic. Examples of relevant questions here include: what would be the criteria for labelling a condition as acceptable for GLGE use? How would these criteria be set up (based on what principles) and who would decide? These issues are again not specific to GLGE; they apply to SGE, as well as to many other genetic and genomic applications (e.g. new born screening). What we have learned from these questions in genetics and genomics in the past is that these are value-laden questions and depend hugely on financial and human resources of regions as well as (political and/or financial) agendas of different stakeholders involved in the discussion. The discussion about enhancement included under the section on SGE (see above) is also relevant here (e.g. potential for injustices, discrimination and eugenics). Another concern should GLGE be used for the enhancement of certain traits is the potential, over the long term, of homogenisation of alleles for these traits, and over the long term a loss of genetic diversity (see also above, Human Genetic Diversity).

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[6] Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine; https://rm.coe.int/168007cf98(Law)

[7] http://portal.unesco.org/en/ev.php-URL_ID=13177&URL_DO=DO_TOPIC&URL_SECTION=201.html

Transparency and concerns over financial and technological imperatives

There are fears that one agenda is to use GLGE more widely beyond severe diseases or even beyond the disease or therapeutic context; for example to use GLGE for enhancement purposes (see above discussion in SGE). If this were realistic, it could be envisaged that a large impetus for some stakeholders may be more financial than to help address medical issues. Of course, conducting science for financial gain is not wrong or bad in and of itself. The problems arise when this goal is hidden or when stakeholders are not completely honest about their motives and conflicts of interest.

BOX 1 Glossary of terms

Term	**Definition**
Clinical use (versus research use)	Throughout this document when we refer to "clinical use" of gene editing, we mean the use of the approach on humans outside of a purely research context. For germ line gene editing, clinical use would imply the use of the approach on germ line cells and the use of those cells to establish a viable pregnancy in a human. The research use of germ line gene editing, on the other hand, means that gene editing is conducted in germ line cells but that these cells are not used to establish a pregnancy.
Human enhancement	A modification aimed at improving human performance and brought about by science-based and/or technology-based interventions in or on the human body. (Nagel, Jensen, 2018)
Gene editing aka Genome Editing Genome modification Gene modification	Approaches used to introduce modifications to DNA in the genome. Such modifications can be done in somatic or germ line cells. Somatic cell genome editing should only change the DNA of the person in which the procedure is performed. Germline genome editing should result in a change in DNA in the person in which the modification is performed as well as all his/her descendants.
Gene therapy	A therapeutic approach involving introducing and/or altering DNA in an organism
Genome	All the DNA of a given organism
Genomics	A field in molecular biology focused on studies of genomes using large-scale DNA analysis to decipher DNA structure and function and intensive use of novel technologies
Germline	Concerning the population of cells that may pass on their genetic material to the progeny; examples are: gametes (e.g. sperm and eggs/oocyte), zygote (fertilized egg) and embryonic cells
Mitochondrial replacement	A technique in which the nucleus is transferred from one embryo (or oocyte before fertilization) with mutated DNA in its mitochondria to an embryo (or oocyte before fertilization) with healthy DNA in the mitochondria. This report does not address this approach specifically although some of the issues overlap.
Mosaicism	An organism who has two or more different sets of DNA. With respect to gene editing for an embryo for example, if all the cells in an embryo are not properly edited, the individual who would develop from that embryo would have some cells "corrected" and some cells uncorrected"
Off-target events	editing DNA at a site other than the target site
Preimplantation genetic diagnosis	An approach allowing for evaluation of genetic make-up of embryos *in vitro* before they are implanted in uterus
Somatic cell	Referring to the cells of the body other than germline cells
Somatic cell nuclear transfer	A technique whereby the nucleus from an adult cell (for example a skin cell) is transferred to an oocyte in which the nucleus was removed
Technological Imperative	The technological imperative is a notion that describes the push to use a new technology based on the novelty of that technology rather than on the actual need to update the technology. A form of this push happens when we change or upgrade our mobile phones to the latest model simply because we want the latest model and not because or previous phone was malfunctioning.

- Some definitions were taken and/or are based on the Reports D2.1, D3.1, D2.4, D3.4 from the SIENNA project (Work Package Leaders HC Howard, Genomics; S. Nagel, Enhancement)

References
(for a full list, please see the long report)

Baylis F (2019) Altered Inheritance CRISPR and the Ethics of Human Genome Editing. Havard University Press,

Bioethics Nuffield Council (2018) Genome Editing and Human Reproduction.

Boggio A, Romano C, Almqvist J (2020) Human Germline Genome Modification and the Right to Science: A Comparative Study of National Laws and Policies. . Cambridge: Cambridge University Press. ,

Church G (2017) Compelling Reasons for Repairing Human Germlines. N Engl J Med 377: 1909-1911

Denier Y (2006) Need or Desire? A Conceptual and Moral Phenomenology of the Child Wish. International Journal of Applied Philosophy 20: 81-95
Iotti M VA, Griffin DK, Groob JS, Brake AJ, Zouves CG, et al. (2019) Estimating demand for germline genome editing: an in vitro fertilization clinic : an in vitro fertilization clinic perspective. The Crisper Journal 2: 304–15

Lander ES, Baylis F, Zhang F, Charpentier E, Berg P, Bourgain C, Friedrich B, Joung JK, Li J, Liu D, Naldini L, Nie JB, Qiu R, Schoene-Seifert B, Shao F, Terry S, Wei W, Winnacker EL (2019) Adopt a moratorium on heritable genome editing. Nature 567: 165-168

Niemiec E, Howard HC (2020) Germline genome editing research: what are gamete donors (not) informed about in consent forms? The CRISPR journal 3: 52-63

Seggers S, Mertes H (2019) Does human genome editing reinforce or violate human dignity? Bioethics 34: 33-40