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Ethics and regulatory considerations for the clinical translation of somatic cell human epigenetic editing

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Altering the human epigenome with gene-editing technology in attempt to treat a variety of diseases and conditions seems scientifically feasible. We explore some of the ethical and regulatory issues related to the clinical translation of human epigenetic editing arguing that such approaches should be considered akin to somatic therapies.

INTRODUCTION

DNA methylation is one mechanism of epigenetic regulation of gene expression and variations in the methylation of the promoter regions of genes are associated with a variety of human diseases. The discovery and application of the CRISPR-Cas gene-editing system has created new opportunities not only for using it to manipulate genomes for therapeutic purposes (Pickar-Oliver and Gersbach 2019), but also to develop therapeutic modalities through methylation-specific epigenome modification (Gjaltema and Rots 2020). Although there is substantial ongoing debate around human genome editing, especially of the germline, there has been relatively little discussion of the ethics and regulation of human epigenome editing (e-GE) of somatic cells using this technology.

There are currently no human trials using e-GE registered in ClinicalTrials.gov, but there are a number of preclinical approaches moving toward human testing in the near future (Hirakawa et al., 2020). Given the tangible possibility of ameliorating a variety of diseases and conditions with e-GE (Table 1), it is critical to examine the related ethical and regulatory issues. To do so, we first address issues related to possible unwanted effects of somatic cell e-GE on the germline. Next, we examine three broad plausible approaches to the clinical translation of somatic cell e-GE: (1) targeting disease genes; (2) augmenting existing therapies; and (3) enhancing phenotypic traits. We then describe some of the scientific and ethical uncertainties of these approaches and their implications. Finally, we discuss some associated regulatory issues.

Unwanted effects of e-GE on germ cells

One of the primary concerns with changes to germ cells is that deleterious changes could be potentially passed on to future generations, for whom germline changes would be irreversible. Such germline modifications are therefore typically unwanted for somatic editing in general, and e-GE in particular.

While a comprehensive scientific review of human e-GE is beyond the scope of this Forum, it is important to note that several lines of evidence suggest that it is unlikely to result in changes that lead to enduring germline effects. First, current evidence suggests that e-GE is unlikely to change the underlying genetic DNA sequence of cells (Gjaltema and Rots 2020). Second, given global resetting of the methylation state in the embryo, inheritable epigenetic modification is unlikely to manifest in offspring. Third, environmentally induced epigenetic modification is transitory and can be reversed by further environmental changes, and is the basis for related recommendations about altering lifestyle and exposure to environmental factors in relation to methylation-based alterations in gene expression related to the development of cancer. Fourth, contemporary approaches to e-GE may only result in transient changes in target cells (Zezulin and Musunuru 2018).

Thus, the lack of enduring germline effects of e-GE avoids some of the ethical concerns raised with human germline genome editing, which are not easily reversible, and where its effects will be passed onto future generations. Accordingly, e-GE of somatic cells ought instead to be considered akin to somatic cell and gene therapy rather than as

Table 1. Three broad approaches to e-GE with potential human applications

Approach	Examples	Method
Correcting disease by targeting the disease genes	Fragile X syndrome Huntington disease spinocerebellar ataxia myotonic dystrophy Huntington disease, spinocerebellar ataxia, and myotonic dystrophy	altering the methylation pattern of gene promotors to restore gene function
	β-thalassaemia sickle cell disease	epigenome modification enables disease correction through derepressing aberrantly silenced genes and upregulating expression of related genes that compensate for the null mutations
	Angelman Prader-Willi Pitt-Hopkins Rett	e-GE could be used to activate the silenced allele
Augment efficacy of existing therapies	tumor suppressors and oncogenes (e.g., EGFR in breast and gastric cancers)	e-GE can reduce oncogenic overexpression, thereby halting or slowing tumor growth
	overcoming drug resistance (e.g., PARP inhibitors, such as rupacarib in ovarian cancer)	the use of e-GE would allow existing drugs to be used in drug-resistant patients and minimize potentially harmful side effects through allowing lower effective doses
Enhancing phenotypic traits	deactivating or activating non-disease genes may enable cell lineage switching or controlled expression of proteins in cells that result in desired phenotypic outcomes (e.g., *erythropoietin for enhanced athletic performance)*	such modalities could enable performance enhancing modifications without the direct use of hormones or drugs

a germline-modifying technology. Nevertheless, as with the use of most experimental clinical interventions in general and existing medication-based approaches to altering the methylome in particular (e.g., azacytidine to treat myelodysplastic syndrome), prudence suggests that the clinical translation of e-GE incorporate methods to caution against pregnancy due to potentially unknown effects on germ cells or the germline.

Potential approaches to clinical translation

Assuming that e-GE is applied to somatic cells, we next explore selected ethical issues of three plausible approaches to the clinical translation of e-GE: (1) targeting disease genes; (2) augmenting existing therapies; and (3) enhancing phenotypic traits. See Table 1 for additional examples.

Targeting disease genes

Altering the methylation pattern of gene promotors to restore gene function could be used in attempt to treat conditions, such as Fragile X syndrome, Huntington disease, spinocerebellar ataxia, and myotonic dystrophy. For example, Fragile X syndrome is caused by hypermethylation of the CGG repeats upstream of the FMR1 promoter, thereby silencing expression of the FMR1 gene. The hypermethylated FMR1 promoter can be targeted via the use of dead-Cas9 fused to TET1, as a potential means of correction (Liu et al., 2018). Alternatively, e-GE might be used to enable disease correction through de-repressing aberrantly silenced genes and upregulating expression of related genes compensating for particular gene mutations. Such an approach may be useful in the treatment of sickle cell disease or thalassemia, by upregulating fetal hemoglobin and thereby minimizing morbidity (Chen et al., 2017).

Correcting major inheritable genetic diseases would be especially beneficial if the intervention could be introduced before those affected become symptomatic. For many such diseases, this will require intervention during early childhood, raising issues about vulnerability and consent. Similar concerns are commonly encountered with other medical interventions in children. A potential benefit of using e-GE is that its effects may be transient or even reversible. If so, it may be possible to discontinue or reverse harmful epigenetic changes. On the other hand, transient effects may also necessitate repeated interventions to maintain desired changes. This necessity could be burdensome for patients and incur significant costs.

Augmenting existing therapies

The epigenome can play a substantial role in cancer with hypermethylation silencing tumor-suppressor expression and hypomethylation resulting in overexpression of oncogenes indicating a potential role for e-GE in cancer treatment if a suitable delivery mechanism can be achieved (Sung and Yim 2020). Moreover, e-GE might enable existing cancer drugs to be used in drug-resistant patients and minimize potentially harmful side effects through allowing lower effective doses. For example, PARP inhibitors (e.g., rupacarib) used in treating ovarian cancer, have reduced efficacy in patients with methylated copies of BRCA1 (Kondrashova et al., 2018); e-GE targeting of this pathway could make those tumors responsive to PARP inhibitors.

The adjunctive use of e-GE in treating cancer could become tied to prescriptions of particular medications to enhance efficacy and reduce side effects from the often toxic medications with which it may be used. However, it is also likely to increase the overall costs of treatment significantly. Additionally, it may create pressures from health insurers and physicians for patients to assume the additional uncertain risks of e-GE when seeking treatment. Such requirements have been imposed in other settings, such as smoking cessation or weight loss before permitting surgery. However, ensuring any mandate is supported by rigorous evidence of clinical benefit over and above cost savings may partially alleviate such concerns.

Enhancing phenotypic traits

Deactivating or activating non-disease genes may enable controlled expression of proteins in cells that result in desired phenotypic outcomes. For example, the erythropoietin gene is regulated by methylation repression (Yin and Blanchard 2000) and it is not beyond imagination that it may be possible to target such genes related to human performance without the traditional use of hormones or small-molecule medications.

The non-medical use of CRISPR-Cas9 to enhance is a potential concern that applies to both genome editing and e-GE, although the issues are subtly different. While the treatment/enhancement divide is conceptually and morally contested (Erler 2017), it is safe to assume that e-GE could be employed for purposes that are not squarely medical, such as promoting expression of erythropoietin genes to aid in athletic capability. This use might confer unfair advantages in competitive sports. The potential reversibility of these changes could alter the cost-benefit calculus as some long-term adverse effects of alternative approaches might be avoided. However, the extent to which such benefits will be realized is unclear and long-term follow-up of recipients is needed to inform this issue.

Uncertainties and implications

While e-GE provides exciting opportunities to benefit human health, the technological barriers should not be understated. The success of any intervention involving e-GE assumes there is a reliable way of identifying risk factors and that they are not under polygenic control or have other redundant pathways that would bypass the edited target. Furthermore, viral vector delivery systems may limit the size of the enzymes that can be employed. Thus, managing expectations will be important to reduce the risks of building unrealistic hopes for miracle cures and creating new direct-to-consumer markets for medical tourism, which has been a persistent problem with stem cell-based interventions, and is emerging with gene therapies (Molteni, 2021). Scientists will need to accurately communicate their research and its uncertainties not only to those considering enrollment in clinical trials of novel approaches and their clinicians whom they trust, but also to the public in ways that foster a realistic sense of the possibilities of e-GE and help reduce the risk of sensationalist coverage resulting in undue high expectations. This may be especially challenging given that the diseases under consideration are rare and lack truly effective treatments.

Finally, the possibility of e-GE gives rise to questions of justice that should be considered in its clinical translation as do other interventions that aim to affect the phenotypic expression of genes resulting in adverse effects. If a particular genetic endowment no longer implies a specific phenotypic outcome, the scope of opportunities widens depending on the presence or absence of e-GE. While this alone does not undermine the idea of natural inequalities, it expands the individual's "genetic potential," and may require re-thinking the disadvantageous nature of certain genotypes. From the perspective of social justice, this might on the one hand be viewed as a positive development, opening up new avenues for correcting "natural" inequalities even if the genome is left untouched. On the other hand, if e-GE is expensive, it might end up replacing some natural inequalities with socioeconomic ones.

Regulatory issues

It now appears likely that somatic cell e-GE could be used in a manner that is consistent with other somatic cell and gene therapies. The apparent lack of germline effects suggests that, even though "gene-editing" technologies are likely to be employed, e-GE ought to be regulated under existing frameworks for clinical research involving novel cell and gene therapeutics, focusing attention on the effects rather than the mechanism of the interventions. In this context, participant safety is paramount throughout the testing and registration life cycle. Despite the inherent uncertainties of any new medical technology, conducting ethically sound e-GE clinical translation research would seem to

be appropriate, especially for serious diseases and conditions where there are no alternative interventions, or where existing treatments are suboptimal.

Having said that, regulators and other policy makers may need to take into account the nature of e-GE and the potential reversibility of changes made to gene expression. Unlike germline modifications, the reversibility of e-GE could make the use of this technology very difficult to detect. This possibility may be a concern when e-GE is used to gain competitive advantage in sporting events. Even if tests can be developed to detect an intervention to the epigenome of targeted cells, they would have to detect edits that have been done previously, and have since been reversed, with residual effects still providing an unfair advantage over other competitors who abided by the rules (assuming these prohibited the use of e-GE for performance enhancement). Regulators may need to consider whether existing frameworks for cell and gene therapies are adequately fit for purpose and, if not, modify them accordingly.

Concluding comments

Epigenome modification offers the prospect of an array of potentially beneficial somatic cell interventions. As germline effects of such interventions currently seem unlikely, somatic cell e-GE may overcome some important scientific and ethical hurdles associated with germline genome editing. Nevertheless, akin to other somatic cell and gene therapies, e-GE has associated ethical and regulatory issues that must be recognized and managed as efforts are taken to assess their true efficacy and safety. While standard approaches to oversight of research and clinical practice are critical, their remit is arguably narrow. It is essential that the larger social and ethical issues outlined above are deliberated upon and appropriate strategies and policies are designed to address them.

WEBSITE RESOURCES

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AUTHOR CONTRIBUTIONS

N.Z. and T.L led the drafting of the manuscript with the core writing team of R.C., A.E., W.L.C., and J.S.. The remaining authors are listed alphabetically and shared equally in contributing substantive comments and editorial work throughout the conceptualization and drafting process.

CONFLICTS OF INTEREST

W.L.C. is a founder of companies associated with gene-editing therapeutic development and has patent applications for gene-editing modalities but not in relation to any of the proposals discussed in this manuscript. J.S. is a member of Merck KGaA's the Bioethics Advisory Panel Stem Cell Research Oversight Committee; is a member of IQVIA's Ethics Advisory Panel; is a member of Aspen Neurosciences Scientific Advisory Board; a member of a Data and Safety Monitoring Board for Merck; is a consultant to Biogen; and has consulted for Portola Pharmaceuticals, Inc. These are unrelated to the material discussed in this manuscript. All other authors have no conflicts of interest to declare.

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