Canadian Journal of Bioethics
Revue canadienne de bioéthique

CRISPR Gene-Therapy: A Critical Review of Ethical Concerns and a Proposal for Public Decision-Making

Victor Lange et Klemens Kappel

Volume 5, numéro 2, 2022

URI : https://id.erudit.org/iderudit/1089787ar
DOI : https://doi.org/10.7202/1089787ar

Aller au sommaire du numéro

Éditeur(s)

Programmes de bioéthique, École de santé publique de l'Université de Montréal

ISSN

2561-4665 (numérique)

Découvrir la revue

Citer cet article

Lange, V. & Kappel, K. (2022). CRISPR Gene-Therapy: A Critical Review of Ethical Concerns and a Proposal for Public Decision-Making. *Canadian Journal of Bioethics / Revue canadienne de bioéthique*, *5*(2), 78–87. https://doi.org/10.7202/1089787ar

Résumé de l'article

CRISPR est actuellement considéré comme l'outil central de la future thérapie génique. Pourtant, de nombreux scientifiques et bioéthiciens de renom ont exprimé des préoccupations éthiques concernant la thérapie génique CRISPR. L'article présente un examen critique des préoccupations concernant la thérapie génique CRISPR telles qu'elles sont exprimées dans la littérature académique courante, ainsi que les réponses que l'on trouve généralement dans cette littérature. Les préoccupations exprimées peuvent être classées en trois catégories selon qu'elles mettent l'accent sur le rapport risque/bénéfice, l'autonomie et le consentement éclairé, ou les préoccupations liées à divers aspects de la justice. Dans la littérature examinée, nous n'avons trouvé aucune objection intrinsèque à la thérapie génique CRISPR, même si beaucoup de ces objections étaient présentes dans les discussions sur l'édition de gènes dans les années 1990. Cet article propose un bref aperçu d'un cadre moral applicable en pratique pour la prise de décision publique sur la thérapie génique CRISPR, et suggère comment un tel cadre pourrait être soutenu. Nous suggérons également que ce cadre devrait régir l'engagement public sur la thérapie génique CRISPR afin de réduire le risque que nous prenions des décisions sur la thérapie génique CRISPR sur la base de perceptions erronées, de vues exagérées du risque ou de vues morales ou religieuses déraisonnables.

Canadian Journal of Bioethics
Revue Canadienne de Bioéthique

V Lange, K Kappel. *Can J Bioeth / Rev Can Bioeth.* 2022;5(2):78-87

ARTICLE (ÉVALUÉ PAR LES PAIRS / PEER-REVIEWED)

CRISPR Gene-Therapy: A Critical Review of Ethical Concerns and a Proposal for Public Decision-Making

Victor Lange[a], Klemens Kappel[a]

Résumé
CRISPR est actuellement considéré comme l'outil central de la future thérapie génique. Pourtant, de nombreux scientifiques et bioéthiciens de renom ont exprimé des préoccupations éthiques concernant la thérapie génique CRISPR. L'article présente un examen critique des préoccupations concernant la thérapie génique CRISPR telles qu'elles sont exprimées dans la littérature académique courante, ainsi que les réponses que l'on trouve généralement dans cette littérature. Les préoccupations exprimées peuvent être classées en trois catégories selon qu'elles mettent l'accent sur le rapport risque/bénéfice, l'autonomie et le consentement éclairé, ou les préoccupations liées à divers aspects de la justice. Dans la littérature examinée, nous n'avons trouvé aucune objection intrinsèque à la thérapie génique CRISPR, même si beaucoup de ces objections étaient présentes dans les discussions sur l'édition de gènes dans les années 1990. Cet article propose un bref aperçu d'un cadre moral applicable en pratique pour la prise de décision publique sur la thérapie génique CRISPR, et suggère comment un tel cadre pourrait être soutenu. Nous suggérons également que ce cadre devrait régir l'engagement public sur la thérapie génique CRISPR afin de réduire le risque que nous prenions des décisions sur la thérapie génique CRISPR sur la base de perceptions erronées, de vues exagérées du risque ou de vues morales ou religieuses déraisonnables.

Mots-clés
biotechnologie, convergence, CRISPR, thérapie génique, principes de niveau intermédiaire, engagement public

Abstract
CRISPR is currently viewed as the central tool for future gene therapy. Yet, many prominent scientists and bioethicists have expressed ethical concerns around CRISPR gene therapy. This paper provides a critical review of concerns about CRISPR gene therapy as expressed in the mainstream academic literature, paired with replies also generally found in that literature. The expressed concerns can be categorised into three types depending on whether they stress risk/benefit ratio, autonomy and informed consent, or concerns related to various aspects of justice. In the reviewed literature, we found no intrinsic objections to CRISPR gene therapy, even though many such objections were present in discussions of gene editing in the 1990s. The paper then proposes a brief outline for a practically applicable moral framework for public decision-making about CRISPR gene therapy and suggests how such a framework might be supported. We also suggest that this framework should govern public engagement about CRISPR gene therapy in order to reduce the risk that we make decisions about CRISPR gene therapy based on misperceptions, inflated views of risk, or unreasonable moral or religious views.

Keywords
biotechnology, convergence, CRISPR, gene therapy, mid-level principles, public engagement

Affiliations
[a] Department of Philosophy, University of Copenhagen, Copenhagen, Denmark
Correspondance / Correspondence: Victor Lange, victorlange.sohrab@gmail.com

INTRODUCTION

CRISPR has consistently been praised as a revolutionary therapeutic tool, in large part because it is precise, easy and cheap to use (1-3). Targets include monogenic diseases such as Sickle Cell and Huntington's disease (4), polygenic diseases such as cancer (5), neurogenerative diseases such as Alzheimer's (6), and psychiatric conditions such as schizophrenia and autism have also been mentioned as potential targets (7,8). Like other novel biotechnologies, CRISPR gene therapy has been the subject of a range of ethical concerns. In this paper, we provide a review of these ethical concerns as they have been presented in the mainstream academic literature, paired with responses to the concerns.[1] While gene therapy has been discussed in bioethics since the 1990s (9), we have focused on literature discussing CRISPR explicitly. In subsequent section, we build on this review to propose a framework for decision-making about CRISPR gene therapy and for public engagement.

ETHICAL CONCERNS OF CRISPR GENE THERAPY

In the following, we review the main objections to CRISPR gene therapy expressed in mainstream academic literature, typically by scientists and bioethicists. We do not intend to cover objections expressed in other venues, such as the press or social media, nor do we offer an opinion survey. We focus instead on CRISPR as this has been at the centre of public attention, though very similar issues may be raised by TALENs, Zinc Finger Nucleases, or future inventions springing out of CRISPR. Moreover, for reasons of space, we have limited our discussion to therapeutic uses of CRISPR, setting aside non-therapeutic uses and enhancement, while acknowledging that enhancement deserves a discussion of its own and that the therapeutic/non-therapeutic distinction is difficult to draw in some cases (10,11). The following sections describes the important concerns found,

[1] We do not distinguish, here, between versions of the CRISPR tool that make double-stranded cuts (such as CRISPR-Cas9) and versions that regulate gene expression without double-stranded cut (such as CRISPRa and CRISPRi).

ISSN 2561-4665

organized according to the *type* of ethical concern, and paired with replies. This highlights our finding that concerns can be naturally divided into three groups: 1) concerns relating to risk/benefit ratio, 2) concerns related to consent and autonomy, and finally 3) concerns related to various aspects of justice.

1. Risk/benefit concerns

The first type of concern stresses that CRISPR gene therapy does not have an acceptable risk/benefit profile (12). This concern has been expressed in multiple ways.

Therapeutic need

One claim is that CRISPR gene therapy is not therapeutically needed as other established and better understood procedures can treat the same diseases but with lower risks. The concern would here be that CRISPR exhibits an unattractive risk-benefit profile given the supply of other more well-known therapeutic procedures. However, despite the relevance of this concern, many commentators stress the exact opposite – that CRISPR gene therapy offers unique therapeutic opportunities (2,11). But things seem different with germline therapy,[2] where it has been widely argued that the combination of in vitro fertilisation (IVF) and preimplantation genetic testing (PGT) offer the same benefits as germline therapy, but with lower risks. By making several embryos and selecting those without the relevant disease alleles, one can gain the same medical benefits as germline cell editing but with lower risks (13). In reply, it has been pointed out that IVF and PGT do *not* offer the same benefits as germline cell editing under the following three scenarios: 1) one of the parents is homozygous with a dominant disease, 2) both of the parents are homozygous with a recessive disease, 3) the disease is polygenic (such as cancer or diabetes) and involves, for example, 20 genes, in which case the couple cannot produce a large enough set of embryos allowing an embryo with the right combination of all alleles to be selected (14). Note here that both scenarios 1 and 2 would be very rare scenarios. Embryos with a homozygous dominant disease allele often are not viable, which means that individuals which such genetic profiles are very rare (15). Concerning scenario 2, the chances of two individuals homozygous with a recessive disease pairing up is very small, assuming random mating. For example, based on the current prevalence of Cystic Fibrosis (an autosomal recessive disease) in the United States, only each 15th year would germline cell editing be needed, otherwise PGT could do the job (15). Concerning scenario 3, one might question whether we have sufficient knowledge of which genes are involved in polygenic diseases, and how these genes interact to use CRISPR gene therapy (16). Such knowledge does not seem to be within close reach, pushing germline as well as somatic cell editing for polygenic diseases out to a more distant future. For work discussing the advantages of germline cell therapy to PGT, see (17,18).

Delivery

Another risk/benefit concern focusses on the delivery of CRISPR. After having delivered CRISPR systems to human retina cells and stem cells, a significant number of the cells either stopped multiplying or died (19,20), which was apparently caused by the cells' cancer defence system (21). Although cell death is not necessarily dangerous to individuals, it is involved in conditions such as autoimmune diseases and neurodegeneration. Delivery hereby poses a relevant safety concern in terms of predisposing individuals to such dangerous conditions. This is a serious concern, but it should be noted first that retina and stem cells may be specifically sensitive to CRISPR interventions: other kinds of human cells, such as bone-marrow cells and many others, have not shown the same sensitivity (22). However, in general, delivery of the CRISPR system to the targeted genome region remain an important challenge to safe therapeutic use (23,24).

Off-target effects

A common worry stresses so-called *off-target effects*, that is, the potential harmful effects of unintended modifications in the targeted genome (25). Since a CRISPR-complex can tolerate a small discrepancy between the sgRNA (the guiding sequence of nucleotides) and the targeted DNA sequence, the CRISPR-complex may edit other than the intended DNA sequence. Off-target effects have been reported several times (26), and may lead to cell death, tumor development, or other unwanted mutations (27,28). Relatedly, even if a CRISPR intervention is successful in only modifying the intended gene(s) in a patient, many genes are multifunctional (or pleiotropic). This means that some disease-causing genes may also have functions that are advantageous to the bearer. For example, a specific variant of the SLC39A gene decreases the risk of Parkinson's disease but increases the risk of schizophrenia and Crohn's disease (13). Fully successful modifications could have unforeseen negative consequences since this could hinder more positive functions of disease related genes. The multifunctional nature of genes might make it hard to assess the medical consequences of modifying some disease relevant genes.

Continuing with this worry, germline therapy would pass modifications on to future generations, giving rise to similar but additional concerns. For example, a specific version of the DARC gene is protective against malaria – yet the same version also makes organisms more vulnerable to HIV. One generation may experience high exposure to HIV and low exposure to malaria, while the exposure might be reversed for the next generation, implying that edits that are beneficial for one generation may be harmful to the next (14).

Notice also that even if a CRISPR gene-therapy intervention modifies the targeted gene(s) in the intended way, the modification may be incomplete with respect to the whole genome of the organism leading to mosaicism in the patient (an individual is genetically mosaic if they have developed from the same zygote and yet carry two or more cell populations with different

[2] Somatic cells (i.e., cells that make up the body of an organism) do not pass modified genetic information to off-spring. By contrast, modifying germline cells (i.e., cells that are involved in reproduction) will lead to their genetic modification being passed to offspring.

genotypes). Mosaicism might be morally worrisome for multiple reasons. First, while mosaicism does not necessarily pose any risk (none of the different genotypes may contain disease-causing genes), the condition has been linked to dangerous conditions such cancer (29). This poses a safety concern in terms of side-effects. Second, since mosaicism involves incomplete modification of the disease relevant gene, it would mean that the subject could still develop the relevant disease since they would still carry the disease relevant gene(s) in one of their genotypes. This poses an efficiency concern (30). Third, mosaicism would also hinder reliable testing of individuals and their genetic disposition to diseases. That is, a test might target one of the individual's genotypes and lead a clinician/geneticist to conclude, on the basis of test, that the subject does not carry the relevant gene, yet be mistaken in this conclusion because the subject's other genotype contained the disease relevant gene. Mosaicism thus also poses a concern of genome testing and ultimately providing adequate treatment for patients (31).

The general reply to concerns like those above would stress advancements in our knowledge of the human genome and in technical feasibility. Whether or when such advancements will be within reach is obviously difficult to say. Yet, CRISPR technologies are continuously improved, for example with regards to off-target effects (32). Using a very specific version of the Cas9-protein (the SpCas9-HF1 version) when editing with the CRISPR-Cas9 system brought off-target effects down to an undetectable level in one study (33). Other improvements have been gained by modifying the strategy for how the Cas9 protein cuts the DNA sequence (34), or by working with a fusion of so-called catalytically inactive Cas9 to FokI nuclease (35). Further, timing the delivery of the CRISPR unit seems to counter mosaicism. Delivering this unit as soon as possible after fertilization seems to decrease this tendency (36). And last of all, new versions of the CRISPR tool, such as CRISPRa and CRISPRi, make epigenetic changes that are reversible (37), a relevant feature since it would allow for potentially undoing possible off-target effects.

2. Consent-related concerns

A second and distinct type of ethical concern is that CRISPR gene therapy on germline cells would be performed without informed consent from the affected individuals, a worry also relevant for somatic cell therapy performed at an early stage. One may ask by what authority the current generation (often parents) could make these decisions? (38)[3]

Two lines of reply are available (39). First, numerous activities and decisions made by parents, or the current generation, can significantly affect future individuals without any consent, e.g., decisions about introduction of technology, political organization, use of natural resources, influence on the environment. Moreover, in a genetic perspective, the behaviour and lifestyle habits of parents may affect the epigenome of their children, likewise without consent. Thus, the absence of informed consent from future individuals cannot plausibly ground an absolute moral constraint on making choices that affect future individuals. Second, the standard procedure in clinical practice for making decisions for individuals who cannot give or withhold informed consent is to approve a therapeutic intervention if and only if the benefits clearly and significantly outweigh the risks. If a safe and efficient CRISPR germline gene therapy could knock out a gene for a monogenic disease such as Sickle cell anaemia or Huntington's chorea in an embryo or the germline, this therapy would pass the test normally employed for consenting to a treatment on behalf of future individuals. Yet, many authors have argued that germline cell interventions are distinctively problematic (40,41). First, germline therapy irreversibly affects individuals: they cannot be reversed by the child as other parental choices (e.g., choice of school). Second, parental choice in influencing the traits of their child is and should remain limited. Parents do not have an absolute and unrestricted right to influence their children in whichever way they want. For example, in the UK, deaf parents are not allowed to choose a deaf child by in vitro fertilization even if they have this preference (40). Third, there are significant off-target effects of germline intervention and often no success in making the desired modification. Though not mentioned directly in any argument against germline gene therapy, one might add that individuals with certain diseases, such as Sickle Cell disease, sometimes state that they would not prefer to be without their disease state (38), and some do not wish to edit the gene out of their own children (42).

In response to these concerns, note first that even if some decisions are in principle reversible, they may well be de facto irreversible for the individuals influenced by them. Examples include the current generation's decisions concerning the use of non-renewable resources, implementation of technology, or the design of political institutions. Second, a trait being irreversible does not imply that it is morally problematic. For example, a pregnant woman opting for a healthy diet irreversibly affects her future child, but this is not morally problematic. Thirdly, germline cell therapy does not rest on the assumption that parents have an unrestricted right to choose whatever trait of their child dictated by their whims. Rather, the moral justification of germline therapy rests on the presumption of a positive contribution that a modified trait adds to future individuals' well-being. Fourth, though off-target effects are a serious concern, research looks promising for avoiding such unintended modifications and effects (as mentioned above). Though we cannot discuss this here, note that some authors have stressed that human rights might be crucial for gene therapy (43,44).

3. Justice-related concerns

The third and last type of ethical concern is centred around the implications CRISPR gene therapy might have for social justice. Social justice in relation to novel biotechnologies refers to a variety of concerns (45). Central among them is *procedural justice*, which concerns the process by which decisions are made – i.e., what stakeholders can influence the decision, whether the procedure is transparent, and other general structures. Policy-decisions concerning CRISPR gene therapy might be procedurally unjust if relevant stakeholders (such as patients) have not been a part of the decision procedure in an appropriate

[3] See also the 2015 Statement on NIH funding of research using gene-editing technologies in human embryos.

way. Several authors have expressed such or related concerns (46). Another justice-related concern focusses on *distributive justice*, i.e., the distribution of benefits and burdens as an outcome of decisions about CRISPR gene therapy. Authors stress in various ways how CRISPR gene therapy may – due to price, location, and other factors – benefit only the already affluent groups in a specific society or globally, and how prior disadvantaged groups may not benefit under such outcomes (47).

In response, note first that justice-related concerns do not point to intrinsic moral difficulties with CRISPR gene therapy. Rather, they represent generic requirements about how health policy decisions are made and how resources are allocated. Second, while procedural justice and fair resource allocation are without doubt important concerns, a medical treatment can be ethically defensible even if provided in an otherwise unfair system. For example, it would seem morally unjustified to disallow an expensive therapy for heart or cancer disease on the ground that due to socio-economic factors only a small percentage of needy patients could afford the therapy (45). Moreover, one could hope that competition and regulation over time would fade out the initial high cost of CRISPR gene therapy. Third, one of the revolutionary aspects of CRISPR is its affordability, suggesting that if CRISPR gene therapy remains expensive this would be for reasons other than the tool itself, but due instead to specific societal, legal, economical arrangements that could be counteracted.

The patenting of CRISPR is a particular justice-related arrangement that has been widely discussed. The two main players in what is known as the “CRISPR patent game” are the University of California at Berkeley (UCB) and the Broad Institute – both have played key roles in developing CRISPR-Cas9 and have been granted patents in different countries (48,49). Many authors have expressed ethical concerns about the current patent situation, often related to procedural and distributive justice (50,51). For example, de Graeff et al. stress the need for including other stakeholders in the patent process than the patentee (52). Similarly, Jasanoff & Hurlbut advocate a platform for decision-making about biotechnology that brings together stakeholders such as patient organizations, pharmaceutical companies, researchers, and research institutes in deciding on patent structure (53). A related discussion focuses on the two fundamental moral motivations for allowing patenting scientific and technological advancements (54,55). First, patenting such advances should encourage scientific and technological progress by providing a fiscal incentive to develop new technologies. Second, it must be ensured that citizens benefit from these advances, which sometimes requires that we intervene in patent structures. A dominant view in the literature is that the current patent structure around CRISPR does not sufficiently satisfy the second motivation. Similarly, some authors have expressed concerns that the two key patentees of CRISPR, UCB and the Broad Institute, have made surrogate companies to which they often grant exclusive rights to use CRISPR. Such patent structures might limit the benefits of CRISPR for citizens (56). Other authors have explored whether patents on CRISPR could be denied altogether on the grounds that concerns for social justice and the public good would demand that no one should have such authority over a technology with therapeutic prospects as great as CRISPR (57).

This concludes our review of ethical objections to CRISPR gene-therapy. We now turn to some general remarks and further implications.

Some conclusions and reflections on the review

First, the reviewed concerns relate to the risk of adverse effects, proper informed consent, legitimate decision processes, fair allocation of health resources, and to socio-economic justice relating to patenting structures. As the ethical approval of any medical therapy, whatever its method of intervention, would plausible require addressing the exact same concerns, but no more than that, our review supports treating CRISPR gene therapy like any other medical therapy. The scientific and the bioethical community have been particularly worried about germline CRISPR gene therapy, and though there are diverging views, many authors stress an “ethical (red) line” between somatic and germline modification (58-63). However, it is not clear from the review what would support this contention. Germline therapy may surely have a worse risk/benefit profile, it may raise special concerns about social justice, and it may require knowledge that we do not yet have. But the basic concerns would be the same.

Secondly, while all the concerns raised are significant, it does not seem that they could not be satisfactorily met in principle or in practice, even if this is not likely to happen in the near future. Third, while the outcome of our review may seem unsurprising, it is noteworthy that a range of *intrinsic objections* found in earlier bioethics debates are absent (64). This includes arguments that some type of intervention is morally wrong because it amounts to “playing god” (65,66), is unnatural (67), or is an expression of a wrongful vision of existence (68). Also absent is what might be called “gut-feeling arguments,” which is the idea that some intervention is morally wrong (or is justifiably believed to be wrong) merely on the grounds that it invokes an instinctive feeling of aversion (69).

Our review has not yet discussed slippery slope arguments (SSAs) although such are regularly mentioned (70,71). Relating to CRISPR, SSAs typically come in three kinds, stressing a slide 1) from somatic gene therapy to germline, 2) from ethically responsible use of embryos to irresponsible use in research, or 3) from gene therapy to genetic enhancement (72). In philosophy, SSAs are generally viewed with suspicion (73,74) and are often dismissed when discussing implementation of different biotechnologies (75,76). It is often unclear what SSAs assert about the slide in question, or what evidence there is that a particular adverse development cannot be prevented by regulatory mechanisms. We have not been able to identify any new SSAs in the CRISPR or gene editing literature that are sufficiently clear about the nature of the slide asserted, or that provide evidence that reasonable measures cannot prevent a slide.

PUBLIC DECISION-MAKING ABOUT CRISPR GENE THERAPY

The CRISPR literature stresses the need for a common framework of ethical principles to guide political, bureaucratic and clinical decision-making concerning CRISPR gene therapy at various levels (77). Based on the consensus in the reviewed literature, it is natural to propose what we will call *the convergence framework* for governing CRISPR gene therapy:

> A specific type of medical intervention is ethically acceptable if and only if it (i) has an acceptable risk/benefit profile, (ii) relevant and proper informed consent can be obtained from affected individuals, and (iii) decisions and policies meet requirement of procedural justice, just allocation of health care resources, etc.

A full explication and defense of the convergence framework is not possible here so a few remarks will have to suffice. We submit that ethical principles for decision-making should meet three desiderata: the principles should be (a) ***feasible*** in that they are manageable in most contexts of political, bureaucratic, and clinical decision-making, (b) ***uncontroversial*** in the sense that they enjoy wide support, and (c) have significant ***theoretical support***. Arguably, the convergence framework meets these criteria.

a) Feasible

The convergence framework specifies midlevel principles, which in our favoured interpretation partially determines a decision-procedure by indicating the moral factors that decision-makers should consider when deciding on policies. Doing so is feasible, unlike trying to logically infer decisions from fully specified ethical principles. This is similar to and borrows from Beauchamp and Childress's influential four principles for biomedical ethics, which were proposed as tools to 'real life' decision-making under time constraints and uncertainty (78). As stated, the framework is obviously vague, but below we suggest that more precise interpretations should be negotiated in part through public deliberation.

b) Uncontroversial

The reviewed academic literature indicates wide support for applying the convergence framework to CRISPR gene therapy. Moreover, several organisations have recommended ethical principles for CRISPR use that closely resemble the convergence framework (79). For example, The U.S. National Academies of Sciences Engineering and Medicine (NASEM) Committee on Human Genome Editing have proposed seven principles for morally responsible use of CRISPR (80).

> **1. Promoting well-being:** *The principle of promoting well-being supports providing benefit and preventing harm to those affected, often referred to in the bioethics literature as the principles of beneficence and nonmaleficence.*
>
> **2. Transparency:** *The principle of transparency requires openness and sharing of information in ways that are accessible and understandable to stakeholders.*
>
> **3. Due care:** *The principle of due care for patients enrolled in research studies or receiving clinical care requires proceeding carefully and deliberately, and only when supported by sufficient and robust evidence.*
>
> **4. Responsible science:** *The principle of responsible science underpins adherence to the highest standards of research, from bench to bedside, in accordance with international and professional norms.*
>
> **5. Respect for persons:** *The principle of respect for persons requires recognition of the personal dignity of all individuals, acknowledgment of the centrality of personal choice, and respect for individual decisions. All people have equal moral value, regardless of their genetic qualities.*
>
> **6. Fairness:** *The principle of fairness requires that like cases be treated alike, and that risks and bene ts be equitably distributed (distributive justice).*
>
> **7. Transnational cooperation:** *The principle of transnational cooperation supports a commitment to collaborative approaches to research and governance while respecting different cultural contexts.*

Each of these principles subsume under one of the three moral dimensions identified in the convergence framework (i.e., the dimension of risk-benefit, autonomy, or justice. For example, principles 1 and 3 seem to concern risk-benefit ratio while principle 5 is interpretable as a concern about autonomy, and principle 6 expresses a basic concern about social justice. Principle 2 might reduce to two types of moral concerns: those of risk-benefit ratio and autonomy.

Compare this to The Nuffield Council of Bioethics (81), which provides a much shorter list of only two ethical principles for regulation and responsible use of CRISPR, specifically applying to germline gene editing.

> **1. The welfare of the future person:** *Gametes or embryos that have been subject to genome editing procedures (or that are derived from cells that have been subject to such procedures) should be used only where the procedure is carried out in a manner and for a purpose that is intended to secure the welfare of and is consistent with the welfare of a person who may be born as a consequence of treatment using those cells.*
>
> **2. Social justice and solidarity:** *The use of gametes or embryos that have been subject to genome editing procedures (or that are derived from cells that have been subject to such procedures) should be permitted only in circumstances in which it cannot reasonably be expected to produce or exacerbate social division or the unmitigated marginalisation or disadvantage of groups within society.*

Principle 1 concerns the welfare of future persons, while principle 2 concerns social justice and solidarity. We find it natural to understand principle 1 as expressing a moral concern about risk-benefit ratio, while principle 2 expresses moral concerns of autonomy and of justice.

From these two frameworks, it is reasonable to draw two conclusions. First, major ethical advisory organs such as NASEM and The Nuffield Council of Bioethics agree in identifying risk-benefit ratio, autonomy, and social justice as the central ethical concerns of CRISPR use. Second, these organisations do not propose any additional type of moral concern as being relevant to the therapeutic use of CRISPR, i.e., moral concerns that cannot be reasonably understood as concerning risk-benefit, autonomy, or justice. Consequently, the convergence framework seems adequate in its moral outlook on the therapeutic use of CRISPR in relation to the independent proposals of these major organisations.

The WHO has also recently published a report on developing global standards for governance and oversight for human genome editing (82). The rapport does not formulate a final set of ethical principles for the use of CRISPR, but stresses instead the values and principles that should guide the development of such regulatory principles and a long line of activities around CRISPR concerning education, research, public engagement, etc. These are values such as inclusiveness, caution, social justice, solidarity and global health justice. One might wonder whether the convergence framework is too thin in the light of the multiple ethical values that the WHO identify as involved in CRISPR. For example, can the framework provide principles for public education on CRISPR? These worries are obviously relevant. In reply, note that the convergence framework is limited in scope and is not intended to govern all activities related to CRISPR, but only whether specific therapeutic use of CRISPR is morally acceptable or not. Second, while further analysis would be relevant here, we do not find that any of the values stressed by the WHO go beyond fundamental concerns about risk-benefit ratio, autonomy, and social justice.

c) Theoretical support

Whether the consensus in the academic literature can be regarded as theoretical support for the framework depends on the highly controversial assumptions that this consensus has emerged from experts who reliably and independently of one another track truth or theoretical plausibility in the moral domain (83). Alternatively, other theoretical support may be found if it can be shown that major ethical theories taken seriously by professional philosophers and ethicists (e.g., varieties of consequentialism, Kantianism, contractualism, and virtue ethics) converge on the framework. Finally, the framework may be defended as public reason principles in the Rawlsian sense. That is, it might be suggested that even when citizens disagree about comprehensive views, reasonable citizens can agree on the convergence framework for the purpose of common decisions about CRISPR (78, note 61 p.383).

Public engagement

The convergence framework might have an important role to play in public engagement on CRISPR gene-therapy. Population surveys indicate that therapeutic uses of CRISPR are supported by a significant majority, whereas non-therapeutic uses, such as enhancement, are rejected. Still, a significant minority rejects the use of therapeutic CRISPR gene-therapy (84-86). Many authors have stressed the need for public engagement, and surveys indicate that citizens concur (44,47,53,86-91). Yet, a common worry is that public engagement leads us to adopt governance structures based on misperceptions, inflated views of risk, or unreasonable moral or religious views (92). A prominent critic is Cass Sunstein, who urges that democratic governments should “respond to people’s values, not to their blunders.” (93, p.126) To counteract this, the convergence framework could be imposed as a constraint on public engagement.

We are aware, of course, that the framework would appear controversial to some citizens. While applying the framework would not prevent any sincerely held view from being freely expressed or publicly debated, it would mean that only reasons stateable or translatable into the framework could ultimately impact legislation and policy making. This would require citizens to sincerely pursue and justify decisions on CRISPR gene therapy in ways compliant with the framework and would limit the types of concerns to which fellow citizens and decision-makers are required to respond.

Given the above, public engagement governed by the convergence framework would be a matter of settling the specific interpretation and contextual weighing of the principles when applied to CRISPR gene therapy. This would, at least to some extent, address the common challenge that the framework is too unspecific and open to various interpretations (92-96). Note also that there are natural anchor points for a reasonable interpretation of the framework: when evaluating CRISPR gene therapies, we should require risk/benefit profiles, consent procedures and social justice that cohere with what we require from other relevantly similar treatments. This would ground our interpretation of the convergence framework in a wider context.

CONCLUSION

In this paper, we provided a critical review of the ethical concerns present in the relevant CRISPR literature and proposed dividing these into three types, i.e., risk/benefit ratio, autonomy and informed consent, and justice related concerns. Our review showed that intrinsic objections to CRISPR gene therapy found in earlier bioethics debates are largely absent. Moreover, we suggested the convergence framework as a guiding scheme for decision-making on CRISPR gene therapy that should both govern and receive a contextually determined and more specific interpretation through public engagement.

Reçu/Received: 19/05/2021

Publié/Published: 13/06/2022

Remerciements

Le travail sur ce document a été généreusement financé par la Fondation Novo Nordisk, dans le cadre du projet Éthique convergente et éthique de la controverse (CEEC). Nous remercions Andreas Christiansen, Bjørn Gunnar Hallsson, Alexander Heape, Katla Hedinsdottir, Nanna Cecilie Halmsted Kongsholm, Gina Labovic, Jonas Aske Dam Rasmussen, Johan Jensen, Niels Gustav Døcker Husum et Annika Andersen pour leurs commentaires et la discussion critique des versions précédentes.

Acknowledgements

Work on this paper was generously funded by the Novo Nordisk Foundation as a part of the project Convergent Ethics and Ethics of Controversy (CEEC). Thanks to Andreas Christiansen, Bjørn Gunnar Hallsson, Alexander Heape, Katla Hedinsdottir, Nanna Cecilie Halmsted Kongsholm, Gina Labovic, Jonas Aske Dam Rasmussen, Johan Jensen, Niels Gustav Døcker Husum, and Annika Andersen for comments and critical discussion of earlier drafts.

Conflits d'intérêts

Aucun à déclarer

Conflicts of Interest

None to declare

Édition/Editors: Erica Monteferrante & Aliya Affdal

Les éditeurs suivent les recommandations et les procédures décrites dans le Code of Conduct and Best Practice Guidelines for Journal Editors de COPE. Plus précisément, ils travaillent pour s'assurer des plus hautes normes éthiques de la publication, y compris l'identification et la gestion des conflits d'intérêts (pour les éditeurs et pour les auteurs), la juste évaluation des manuscrits et la publication de manuscrits qui répondent aux normes d'excellence de la revue.

The editors follow the recommendations and procedures outlined in the COPE Code of Conduct and Best Practice Guidelines for Journal Editors. Specifically, the editors will work to ensure the highest ethical standards of publication, including: the identification and management of conflicts of interest (for editors and for authors), the fair evaluation of manuscripts, and the publication of manuscripts that meet the journal's standards of excellence.

Évaluation/Peer-Review: Donna Dickenson & Jacob S. Sherkow

Les recommandations des évaluateurs externes sont prises en considération de façon sérieuse par les éditeurs et les auteurs dans la préparation des manuscrits pour publication. Toutefois, être nommé comme évaluateurs n'indique pas nécessairement l'approbation de ce manuscrit. Les éditeurs de la *Revue canadienne de bioéthique* assument la responsabilité entière de l'acceptation finale et de la publication d'un article.

Reviewer evaluations are given serious consideration by the editors and authors in the preparation of manuscripts for publication. Nonetheless, being named as a reviewer does not necessarily denote approval of a manuscript; the editors of *Canadian Journal of Bioethics* take full responsibility for final acceptance and publication of an article.

REFERENCES

1. Cai L, Fisher AL, Huang H, Xie Z. CRISPR-mediated genome editing and human diseases. Genes & Disease. 2016;3(4):244-51.
2. Cox DB, Platt RJ, Zhang F. Therapeutic genome editing: prospects and challenges. Nature Medicine. 2015;21(2):121-31.
3. Doudna JA, Charpentier E. The new frontier of genome engineering with CRISPR-Cas9. Science. 2014;346(6213):1258096.
4. Shin JW, Kim KH, Chao MJ, et al. Permanent inactivation of Huntington's disease mutation by personalized allele-specific CRISPR/Cas9. Human Molecular Genetics. 2016;25(20):4566-76.
5. Sánchez-Rivera FJ, Jacks T. Applications of the CRISPR-Cas9 system in cancer biology. Nature Reviews Cancer. 2015;15(7):387-95.
6. Rohn TT, Kim N, Isho NF, Mack JM. The potential of CRISPR/Cas9 gene editing as a treatment strategy for Alzheimer's Disease. Journal of Alzheimer's disease & Parkinsonism. 2018;8(3):439.
7. Zhuo C, Hou W, Hu L, Lin C, Chen C, Lin X. Genomic editing of non-coding RNA genes with CRISPR/Cas9 ushers in a potential novel approach to study and treat schizophrenia. Frontiers in Molecular Neuroscience. 2017;10:28.
8. Wang P, Lin M, Pedrosa E, et al. CRISPR/Cas9-mediated heterozygous knockout of the autism gene CHD8 and characterization of its transcriptional networks in neurodevelopment. Molecular Autism. 2015;6:55.
9. Holtug N. Altering humans—the case for and against human gene therapy. Cambridge Quarterly of Healthcare Ethics. 1997;6(2):157-74.
10. Giubilini A, Sanyal S. The ethics of human enhancement. Philosophy Compass. 2015;10(4):233-43.
11. Mo O. CRISPR-Cas9 human genome editing: challenges, ethical concerns and implications. Journal of Clinical Research and Bioethics. 2015;6(6).

12. Brokowski C, Adli M. CRISPR ethics: moral considerations for applications of a powerful tool. Journal of Molecular Biology. 2019;431(1):88-101.
13. Lander ES, Baylis F, Zhang F, et al. Adopt a moratorium on heritable genome editing. Nature. 2019;567(7747):165-8.
14. Gyngell C, Douglas T, Savulescu J. The ethics of germline gene editing. Journal of Applied Philosophy. 2017;34(4):498-513.
15. Viotti M, Victor AR, Griffin DK, et al. Estimating demand for germline genome editing: an in vitro fertilization clinic perspective. The CRISPR Journal. 2019;2(5):304-15.
16. Greely HT. Human germline genome editing: an assessment. The CRISPR Journal 2019;2(5):253-65.
17. v. Hammerstein AL, Eggel M, Biller-Andorno N. Is selecting better than modifying? An investigation of arguments against germline gene editing as compared to preimplantation genetic diagnosis. BMC Medical Ethics. 2019;20:83.
18. Ranisch R. Germline genome editing versus preimplantation genetic diagnosis: Is there a case in favour of germline interventions? Bioethics. 2020;34(1):60-9.
19. Ihry RJ, Worringer KA, Salick MR, et al. p53 inhibits CRISPR-Cas9 engineering in human pluripotent stem cells. Nature Medicine. 2018;24(7):939-46.
20. Haapaniemi E, Botla S, Persson J, Schmierer B, Taipale J. CRISPR-Cas9 genome editing induces a p53-mediated DNA damage response. Nature Medicine. 2018;24(7):927-30.
21. Memi F, Ntokou A, Papangeli I. CRISPR/Cas9 gene-editing: Research technologies, clinical applications and ethical considerations. Seminars in Perinatology. 2018;42(8):487-500.
22. Fellmann C, Gowen BG, Lin PC, Doudna JA, Corn JE. Cornerstones of CRISPR-Cas in drug discovery and therapy. Nature Reviews Drug Discovery. 2017;16(2):89-100.
23. Lino CA, Harper JC, Carney JP, Timlin JA. Delivering CRISPR: a review of the challenges and approaches. Drug Delivery. 2018;25(1):1234-57.
24. Gori JL, Hsu PD, Maeder ML, Shen S, Welstead GG, Bumcrot D. Delivery and specificity of CRISPR-Cas9 genome editing technologies for human gene therapy. Human Gene Therapy. 2015;26(7):443-51.
25. Stella S, Montoya G. The genome editing revolution: A CRISPR-Cas TALE off-target story. Bioessays. 2016;38 (Suppl 1):S4-S13.
26. O'Geen H, Yu AS, Segal DJ. How specific is CRISPR/Cas9 really? Current Opinion in Chemical Biology. 2015;29:72-8.
27. Carroll D. Collateral damage: benchmarking off-target effects in genome editing. Genome Biology. 2019;20(1):114.
28. Ma Y, Zhang L, Huang X. Genome modification by CRISPR/Cas9. The FEBS Journal. 2014;281(23):5186-93.
29. Jacobs KB, Yeager M, Zhou W, et al. Detectable clonal mosaicism and its relationship to aging and cancer. Nature Genetics. 2012;44(6):651-8.
30. Lamas-Toranzo I, Galiano-Cogolludo B, Cornudella-Ardiaca F, et al. Strategies to reduce genetic mosaicism following CRISPR-mediated genome edition in bovine embryos. Scientific Reports. 2019;9:14900.
31. Mehravar M, Shirazi A, Nazari M, Banan, M. Mosaicism in CRISPR/Cas9-mediated genome editing. Developmental Biology. 2019:445(2):156-162.
32. Tan EP, Li Y, Velasco-Herrera Mdel C, Yusa K, Bradley A. Off-target assessment of CRISPR-Cas9 guiding RNAs in human iPS and mouse ES cells. Genesis. 2015;53(2):225-36.
33. Kleinstiver BP, Pattanayak V, Prew MS, et al. High-fidelity CRISPR-Cas9 nucleases with no detectable genome-wide off-target effects. Nature. 2016;529(7587):490-5.
34. Ran FA, Hsu PD, Wright J, Agarwala V, Scott DA, Zhang F. Genome engineering using the CRISPR-Cas9 system. Nature Protocols. 2013;8(11):2281-308.
35. Guilinger JP, Thompson DB, Liu DR. Fusion of catalytically inactive Cas9 to FokI nuclease improves the specificity of genome modification. Nature Biotechnology. 2014;32(6):577-82.
36. Hashimoto M, Yamashita Y, Takemoto T. Electroporation of Cas9 protein/sgRNA into early pronuclear zygotes generates non-mosaic mutants in the mouse. Developmental Biology. 2016;418(1):1-9.
37. Kampmann M. CRISPRi and CRISPRa screens in mammalian cells for precision biology and medicine. ACS Chemical Biology. 2018;13(2):406-16.
38. Ormond KE, Mortlock DP, Scholes DT, et al. Human germline genome editing. American Journal of Human Genetics. 2017;101(2):167-76.
39. Smith KR, Chan S, Harris J. Human germline genetic modification: scientific and bioethical perspectives. Archives of Medical Research. 2012;43(7):491-513.
40. Smolenski J. CRISPR/Cas9 and germline modification: new difficulties in obtaining informed consent. Amercian Journal of Bioethics. 2015;15(12):35-7.
41. Habermas J. The Future of Human Nature. Cambridge, England: Polity; 2003.
42. Check Hayden E. Should you edit your children's genes? Nature. 2016;530(7591):402-5.
43. Liao SM. Designing humans: A human rights approach. Bioethics. 2019;33(1):98-104.
44. Halpern J, O'Hara SE, Doxzen KW, Witkowsky LB, Owen AL. Societal and ethical impacts of germline genome editing: how can we secure human rights? The CRISPR Journal. 2019;2(5):293-8.
45. Hunter D. How to object to radically new technologies on the basis of justice: the case of synthetic biology. Bioethics. 2013;27(8):426-34.
46. Jasanoff S, Hurlbut JB, Saha K. Democratic governance of human germline genome editing. The CRISPR Journal. 2019;2(5):266-71.

47. Hildebrandt CC, Marron JM. Justice in CRISPR/Cas9 research and clinical applications. AMA Journal of Ethics. 2018;20(9):E826-33.
48. Ledford H. CRISPR, the disruptor. Nature. 2015;522(7554):20-4.
49. Feeney O, Cockbain J, Morrison M, Diependaele L, Van Assche K, Sterckx S. Patenting foundational technologies: lessons from CRISPR and other core biotechnologies. Amercian Journal of Bioethics. 2018;18(12):36-48.
50. Contreras JL. Is CRISPR different? considering exclusivity for researchtools, therapeutics, and everything in between. American Journal of Bioethics. 2018;18(12):59-61.
51. Cook-Deegan R. CRISPR patents: aspiring to coherent patent policy. American Journal of Bioethics. 2018;18(12):51-4.
52. de Graeff N, Dijkman LE, Jongsma KR, Bredenoord AL. Fair governance of biotechnology: patents, private governance, and procedural justice. American Journal of Bioethics. 2018;18(12):57-9.
53. Jasanoff S, Hurlbut JB. A global observatory for gene editing. Nature. 2018;555(7697):435-7.
54. Boggio A, Ho CWL. The human right to science and foundational technologies. American Journal of Bioethics. 2018;18(12):69-71.
55. Farrelly C. Gene patents and the social justice lens. American Journal of Bioethics. 2018;18(12):49-51.
56. Contreras JL, Sherkow JS. CRISPR, surrogate licensing, and scientific discovery. Science. 2017;355(6326):698-700.
57. Capps B, Mulvihill JJ, Joly Y, Lysaght T. The view of CRISPR patents through the lens of solidarity and the public good. American Journal of Bioethics. 2018;18(12):54-6.
58. Baumann M. CRISPR/Cas9 genome editing – new and old ethical issues arising from a revolutionary technology. NanoEthics. 2016;10(2):139-59.
59. Schultz-Bergin M. Is CRISPR an ethical game changer? Journal of Agricultural and Environmental Ethics. 2018;31(2):219-38.
60. Scherz P. The mechanism and applications of CRISPR-Cas9. The National Catholic Bioethics Quarterly. 2017;17(1):29-36.
61. Bosley KS, Botchan M, Bredenoord AL, et al. CRISPR germline engineering – the community speaks. Nature Biotechnology. 2015;33(5):478-86.
62. Vasiliou SK, Diamandis EP, Church GM, et al. CRISPR-Cas9 system: opportunities and concerns. Clinical Chemistry. 2016;62(10):1304-11.
63. Werner-Felmayer G, Shalev C. Human germline modification—a missing link. American Journal of Bioethics. 2015;15(12):49-51.
64. Macintosh KL. Enhanced Beings: Human Germline Modification and the Law. Cambridge: Cambridge University Press; 2018.
65. Coady CAJ. Playing god. In: Savulescu J, Bostrom N, editors. Human Enhancement: Oxford University Press; 2009. p. 155-80.
66. Held V. Feminist transformations of moral theory. Philosophy and Phenomenological Research. 1990;50(suppl):321-44.
67. Sheehan M. Making sense of the immorality of unnaturalness. Cambridge Quarterly of Healthcare Ethics. 2009;18(2):177-88.
68. Sandel MJ. The case against perfection. The Atlantic. 2004;293(3):50.
69. Kass LR. The wisdom of repugnance: why we should ban the cloning of humans. The New Republic. 1997;216(22):17-26.
70. Macpherson I, Roqué MV, Segarra I. Ethical challenges of germline genetic enhancement. Frontiers in Genetics. 2019;10:767.
71. Launis V. Human gene therapy and the slippery slope argument. Medicine, Health Care, and Philosophy. 2002;5(2):169-79.
72. Cavaliere G. Background paper: the ethics of human genome editing. WHO Expert Advisory Committee on Developing Global Standards for Governance and Oversight of Human Genome Editing. 2019.
73. Enoch D. Once you start using slippery slope arguments, you're on a very slippery slope. Oxford Journal of Legal Studies. 2001;21(4):629-47.
74. Spielthenner G. A logical analysis of slippery slope arguments. Health Care Analysis. 2009;18(2):148-63.
75. Walton D. The slippery slope argument in the ethical debate on genetic engineering of humans. Science and Engineering Ethics. 2016;23(6):1507-28.
76. Callies DE. The slippery slope argument against geoengineering research. Journal of Applied Philosophy. 2019;36(4):675-87.
77. Sherkow JS. Controlling CRISPR through law: legal regimes as precautionary principles. The CRISPR Journal. 2019;2(5):299-303.
78. Beauchamp TL, Childress JF. Principles of Biomedical Ethics. 7th ed. New York: Oxford University Press; 2013.
79. Brokowski C. Do CRISPR germline ethics statements cut it? The CRISPR Journal. 2018;1(2):115-125.
80. National Academies of Sciences, Engineering, and Medicine. Human Genome Editing: Science, Ethics, and Governance. Washington, DC: The National Academies Press; 2017.
81. Nuffield Council on Bioethics. Genome Editing and Human Reproduction: Social and Ethical Issues. London: Nuffield Council on Bioethics; 2018
82. WHO Expert Advisory Committee on Developing Global Standards for Governance and Oversight of Human Genome Editing. Human Genome Editing: Recommendations. Geneva: World Health Organization; 2021.

83. Goldman AI. Experts: which ones should you trust? Philosophy and Phenomenological Research. 2001;63(1):85-110.
84. Critchley C, Nicol D, Bruce G, Walshe J, Treleaven T, Tuch B. Predicting public attitudes toward gene editing of germlines: the impact of moral and hereditary concern in human and animal applications. Frontiers in Genetics. 2018;9:704.
85. Gaskell G, Bard I, Allansdottir A, et al. Public views on gene editing and its uses. Nature Biotechnology. 2017;35(11):1021-3.
86. Scheufele DA, Xenos MA, Howell EL, Rose KM, Brossard D, Hardy BW. U.S. attitudes on human genome editing. Science. 2017;357(6351):553-4.
87. Saha K, Hurlbut JB, Jasanoff S, et al. Building capacity for a global genome editing observatory: institutional design. Trends in Biotechnology. 2018;36(8):741-3.
88. Hurlbut JB, Jasanoff S, Saha K, et al. Building capacity for a global genome editing observatory: conceptual challenges. Trends in Biotechnology. 2018;36(7):639-41.
89. Durant J. Participatory technology assessment and the democratic model of the public understanding of science. Science and Public Policy. 1999;26(5):313-9.
90. Gastil J. Designing public deliberation at the intersection of science and public policy. In: Hall Jamieson K, Kahan DM, Scheufele DA, editors. The Oxford Handbook of the Science of Science Communication; 2017. p. 233-42.
91. McCaughey T, Budden DM, Sanfilippo PG, et al. A need for better understanding is the major determinant for public perceptions of human gene editing. Human Gene Therapy. 2019;30(1):36-43.
92. Benston S. Everything in moderation, even hype: learning from vaccine controversies to strike a balance with CRISPR. Journal of Medical Ethics. 2017;43(12):819-23.
93. Sunstein CR. Laws of Fear: Beyond the Precautionary Principle. Cambridge: Cambridge University Press; 2005.
94. Clouser KD, Gert B. A critique of principlism. The Journal of Medicine and Philosophy. 1990;15(2):219-36.
95. DeGrazia D. Moving forward in bioethical theory: theories, cases, and specified principlism. The Journal of Medicine and Philosophy. 1992;17(5):511-39.
96. Strong C. Specified principlism: What is it, and does it really resolve cases better than casuistry? The Journal of Medicine and Philosophy. 2000;25(3):323-41.