The CRISPR Journal
Volume 00, Number 00, 2024

DOI: 10.1089/crispr.2024.0021

The CRISPR Journal

ORIGINAL ARTICLE

Challenging the Boundaries Between Treatment, Prevention, and Enhancement in Human Genome Editing

Margaret Waltz,[1,*] Rebecca L. Walker,[1,2] Michael A. Flatt,[3] Douglas MacKay,[4] John M. Conley,[5] Eric T. Juengst,[1,†] and R. Jean Cadigan[1,†]

Abstract

Traditional distinctions between treatment and enhancement goals for human genome editing (HGE) have animated oversight considerations, yet these categories have been complicated by the addition of prevention as a possible target for HGE applications. To assess the role these three categories might play in continued HGE governance efforts, we report on interviews with genome editing scientists and governance group members. While some accepted traditional distinctions between treatment and enhancement and rejected the latter as unacceptable, others argued that the concept of enhancement is largely irrelevant or not as morally problematic as suggested. Others described how preventive goals for HGE create gray zones where prevention and enhancement may be difficult to distinguish, which may stymie uses of HGE. We conclude by discussing the governance implications of these various understandings of treatment, prevention, and enhancement as HGE research moves beyond the treatment of serious disease to embrace longer range preventive goals.

Introduction

In the literature on the governance of human genome editing (HGE) research, it is common to draw a distinction between uses of these technologies that address health and welfare deficits and uses that aim at further improvements. One hope for such a distinction would be to provide a way to trace the ethically salient limits of HGE, enabling scientists and those involved in governance to embrace its uses to address disease and disability and resist expansive uses as ethically problematic. Indeed, the idea that there is both an ethical and conceptual distinction between "treatment" on the one hand and "enhancement" on the other has decades-old roots in the bioethical and policy discussion of human genetic engineering.[1,2] Moreover, the recent addition of prevention as a possible target for HGE applications[3–5] creates a third category that begs for a distinction. However, attempts to draw distinctions have yielded various articulations. For instance, enhancement interventions have been defined as changes that go beyond the norm[6] or as applications of gene editing that are opposed to disease or medical applications.[3,7] However, such medical applications can include both treatment and prevention efforts.[3,8] In addition, some have questioned whether prevention efforts can be a form of enhancement or minimally paving the way for acceptance of enhancement interventions given the difficulty in drawing distinctions.[8]

Over the years, these distinctions have been analyzed, criticized, and defended in multiple ways. In some scholarly circles, for instance, the distinction between treatment and enhancement is viewed as an obsolete attempt at creating boundaries, no longer useful to the practical governance of HGE.[6,9,10] Despite such critiques, this distinction continues to animate public attitudes toward HGE[11,12] and still appears in national and international governance deliberations as a significant consideration in the oversight of this technology.[3–5]

In assessing the role that the categories of treatment, prevention, and enhancement (hereafter TPE) might play in HGE governance, a first step is to understand the ways that two groups—scientists actively involved in research

[1]*Department of Social Medicine and Center for Bioethics, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA;* [2]*Department of Philosophy, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA;* [3]*Department of Sociology, Cuyahoga Community College, Cleveland, Ohio, USA;* [4]*Department of Public Policy and Center for Bioethics, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA; and* [5]*School of Law, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA.*
[†]*Eric T. Juengst and R. Jean Cadigan should be considered joint senior author.*

*Address correspondence to: *Margaret Waltz, Department of Social Medicine and Center for Bioethics, University of North Carolina at Chapel Hill, 333 South Columbia Street, Chapel Hill, NC, 27599, USA,* E-mail: margaret_waltz@med.unc.edu

that uses genome editing ("scientists") and members of groups that have developed governance proposals for HGE ("governance group members")—interpret these concepts. Both groups will influence the direction of HGE research, either through on-the-ground research decisions or broader governance recommendations. To date, however, there has been relatively little research on the ways that genome editing scientists and governance group members currently interpret TPE distinctions, or analysis of what those interpretations might mean for the governance of HGE research. In this article, we report on interviews with these two groups, analyze how they discussed TPE, and draw governance implications from their views.

Materials and Methods

Potential scientist interviewees were identified by literature searches or conference presentations on HGE research, including its translational pathway to develop gene editing science with the eventual goal of use in humans.[a] Governance group members were identified by rosters of, at the time, active HGE oversight groups or other organized efforts to influence policy, such as deliberative democracy efforts.[b] Some governance group members were also genome editing scientists, falling into a "hybrid" category. We recruited eligible scientists and governance group members *via* e-mail. We then emailed a study information sheet containing the basic elements required for informed consent to those who agreed to an interview and obtained verbal consent just before the start of the interview. The Institutional Review Board (IRB) at the University of North Carolina-Chapel Hill determined that our study met qualifications for exemption from Common Rule oversight.

We conducted interviews from April 2021 through January 2023. Interview topics included views on nonheritable (somatic cell) and heritable (germline) HGE and how human and nonhuman animal genome editing should be governed. We also asked about uses of and distinctions between TPE. We chose to use the terms "treatment" and "prevention" in the interviews as opposed to "disease applications" of gene editing as the latter can refer to treatment and/or prevention. Using TPE allowed us to better capture the views of our interviewees on any distinctions between the three. The interviews were conducted and recorded *via* Zoom and lasted approximately 60 min. Recordings were transcribed for analysis.

We used memoing as our main analytic approach to the transcripts.[13,14] Our interview guide served as a template to facilitate analytic memoing, and after reviewing a subset of interview transcripts, we revised the template based on emerging themes. Team members were trained on how to complete the memo templates, and to facilitate consistency across memos, we met frequently as a team to discuss questions and progress. For each memo theme, we summarized the relevant information contained in the transcripts, how the information related to other themes, and tracked representative quotes and their context. For the results presented in this article, we analyzed data related to TPE across all transcripts. After meeting as a group to discuss themes emerging from the memos related to TPE, one author (M.W.) then returned to the transcripts to identify further illustrative quotes related to these categories and presented these quotes to the group to confirm their relevance.

Results

Table 1 reports the demographic characteristics of the 92 interviewees included in this analysis. Our interviewees were primarily scientists (81), 22 of whom also participated in a

Table 1. Demographics of interviewees (n = 92)

	Variable	*Frequency*	*Percentage*
Interviewee Group	Scientist	59	64.1
	Scientist in Governance Group	22	23.9
	Governance Group Member	11	12.0
Institution Type	Academic	73	79.3
	Industry	7	7.6
	Academic and Industry	9	9.8
	Other	3	3.3
Region	Africa	3	3.3
	Asia	9	9.8
	Europe	33	35.9
	Middle East	1	1.1
	North America	38	41.3
	Oceana	6	6.5
	South America	2	2.2
Degree	PhD	76	82.6
	MD	4	4.3
	MD, PhD	6	6.5
	JD	1	1.1
	Master's	3	3.3
	Bachelor's	2	2.2

[a]*We conducted a literature search on PubMed using the search terms "gene edit," "genome edit," "CRISPR," "gene therapy," "zinc fingers," or "TALENS" and "prevent" or "enhance" for the past 5 years at the time of the search. We limited publications to those written in English. We included authors of publications of interest for our study goals (gene editing that could have incidental enhancement implications per the bioethics literature), such as muscle wasting, cognition, pain suppression, and metabolism. We captured the contact information of lead and senior authors for whom we could find an email address. As our project continued, we periodically updated the list of scientists who met our eligibility criteria. For conference presentations, we attended conferences related to human genetics more generally and gene editing specifically (e.g., American Society of Human Genetics annual meetings, International Summits on Human Genome Editing). We recorded potential interviewees based on the criteria described above relating to our study goals. We purposefully selected authors to contact to yield an international sample of gene editing scientists.*

[b]*We compiled a list of members from groups such as the WHO Expert Advisory Committee on Developing Global Standards for Governance and Oversight of Human Genome Editing and the International Commission on the Clinical Use of Human Germline Genome Editing. We then purposefully sampled members to yield an international sample of governance group members and continued to recruit until we had representation across various groups.*

genome editing governance group (hybrid interviewees). We interviewed an additional 11 nongenome editing scientist governance group members who included ethicists, lawyers, and social scientists. Most interviewees held PhDs (76). They worked predominantly in North America (38) or Europe (33). Most (73) worked solely in academia, 7 worked solely in industry, and 9 worked in both academia and industry.

In the sections below, we describe four dominant themes that emerged regarding respondents' views of TPE, which have implications for the normative and conceptual distinctions between these categories and their usefulness for governance.

Boundaries are identifiable and meaningful

Some interviewees adopted, at least implicitly, the traditional line of thinking about the boundaries between treatment and enhancement uses of HGE, finding the two categories to be easy to distinguish and thus conceptually unproblematic. For instance, one interviewee said that enhancement "should be rigidly prohibited" because:

> "It's not a matter of disease. It's a matter of enhancement. Currently, people are worried about the possible use of genome editing technology to correct the genes that involve our strength, our intelligence. It's not related to our health. It's kind of our capability or ability or our intelligence" [Scientist (S) 1].

Another scientist also only took issue with enhancement, saying:

> "Enhancement has, to me, rather dangerous connotations. I would say these are the things that we should ban in the beginning. So, just changing the height of the human or [focusing on the] quote unquote 'characteristic' that our society would say or typically consider to be the most attractive, I think" (S2).

Echoing this sentiment, an interviewee drew a line between gene editing for curing disease and gene editing for enhancement, saying, "Disease is one thing. If you can cure a family from Huntington's chorea, fine. It may be worth the risk of changing an embryo. It may be." But when it comes to "funny things," like allowing people to see more colors, this person said, "I'm totally against [enhancements] . . ." (S3).

Often interviewees' rejection of enhancement appeared to reflexively endorse received wisdom about TPE distinctions, alluding to how enhancement involves cheating or playing God. One scientist, for instance, said that enhancement is "not justified," and continued:

> "There you're getting into selection of human beings like you select mice. It's equivalent to performance enhancing drugs, and that's not good. And, yeah, it's banned and it should be banned. So, yeah, no justification for that in my mind. That's when you are starting to play God, up there with, you know, the puppets" (S4).

Others referred to "designer babies," like an interviewee who said that for heritable genome editing, "I will always be totally opposed to genome germline editing in humans, which designer babies are going to be the ones to have blue eyes, blond hair, perfect 6 foot 2 genetically lean person. You know, if that's what you want your kid to be, I'm opposed to that" (S5).

Boundaries may be identifiable but are irrelevant

A small group of interviewees thought that regardless of whether enhancement is clearly defined, concerns over possible enhancement applications are largely irrelevant given that those applications are scientifically impossible. One such interviewee said:

> "I think the enhancement, it's overblown. You're not gonna be able to – You know, you can make your kids more attractive by straightening their teeth. You can't make them smarter by gene therapy. We don't know which road to build for that" (S6).

Another scientist went into more detail about why scientists would not be able to accomplish enhancements using gene editing:

> "To be honest, I think the whole enhancement arena is a bit of a joke. And it's based off assumptions . . . I mean, let's try and list the things that would be considered enhancement: intelligence, eye color, height, physique. Those are all things that are multifactorial and polygenic. And so, it's almost unfair to compare them to single gene disorders because single gene disorders, and the correction thereof, is within the realm of current possibility and capability of the technology. Multifactorial polygenic disorders and editing of multiple genes at once is not currently available. We can't do that" (S7).

For this interviewee, enhancement is not something to worry about because it is presently impossible, but the comparison of potential enhancements to treatments for single gene disorders is seen as unfair and, in that way, a distraction from what matters for HGE.

While some interviewees argued that enhancements could not be accomplished *now*, others were skeptical that enhancements would *ever* be possible given the complexity of causal factors involved in complex traits. Summarizing this point, one interviewee saw potential ethical issues related to enhancement, but did not think gene editing science could ever get there:

> "Let's say if parents wanted children who were tall and smart, or more like healthy or something, could there be ethical ramifications to doing gene editing? Yes, there absolutely could be. This is exactly why there were all these issues with eugenics, and this is the same concept. However, we don't know what are genes that influence things like personality or other aspects that, for example, that control intelligence and things like that. It's very complicated and clearly it's not due to a single gene. So, therefore, if you were able to figure out all the puzzle pieces that control something like intelligence or height or things like that, yes, it could be problematic. But, I don't think we'll ever figure those things out. Those are not Mendelian traits" (S8).

Overall, for these interviewees, discussions of enhancement hit a dead end. Why distract from the important

potential of HGE by discussing something that is "overblown," a "joke," and not possible? Because we cannot enhance someone, worry about enhancement is wasted time at best and unfair to achievable positive uses of HGE at worst.

Boundaries may be identifiable but are not normative

Challenging the idea that enhancements through gene editing are irrelevant, other respondents argued that enhancements through gene editing are inevitable as many enhancements are currently permitted. In this way, although the boundaries between treatment and enhancement may be identifiable, they are not normative for governance. To illustrate this point, some referred to commonplace, "legitimate" interventions like cosmetic and plastic surgery. For instance, one interviewee said:

> "I don't know if we can draw a line between what is a disease and what is an enhancement. Right now, we have medical procedures that are completely enhancement. If you want to change anything about your body, you can go to a surgeon, and they'll do it for you. But you're an adult and you can give consent and that is legitimate in the eyes of society right now. I think the same thing is going to end up applying to gene editing. I don't see why it wouldn't" [Hybrid (H) 9].

Echoing this sentiment, another scientist commented:

> "When I'm thinking about the word enhancement, I'm thinking about physical or cosmetic enhancement . . . Personally, I wouldn't support it. However, I could see that a lot of people would be very happy to do it because the population goes through all types of enhancements all the time. We have cosmetic surgery and plastic surgeries, etcetera" (S10).

While this scientist may not personally support enhancement, through current methods or gene editing, they perceive that society's acceptance of cosmetic and plastic surgery may trickle into the acceptance of enhancements through HGE. Another interviewee noted a similar trickle, saying that a "demand" for enhancements through gene editing may begin and become normalized "just like we see in cosmetic surgery right now" [Governance Member (G) 11]. This interviewee continued, referencing cataract surgery, which they see as a treatment that happens to result in enhancement by improving an individual beyond their baseline, saying about the new vision: "It's not superhuman. It's not even the best among humans, but it's certainly better than [baseline]." (G11).

Rather than lamenting that gene editing enhancements are inevitable, others offered a positive spin on enhancement uses of HGE. Regarding somatic genome editing, one such interviewee commented:

> "You can always argue where does therapy start and enhancement end or the other way around . . . I'm actually quite liberal about this. When you talk about – I'm staying in the area of somatic genome editing where any enhancement or therapeutic application . . . would be limited to a person and maybe limited in time and to a certain organ or phenotype. And so, here we take all kinds of enhancing drugs. We take all kinds of measures to enhance ourselves. And as long as the risk of genome editing is as low as the risk of these drugs, for example. We know about the risks, and I have personally not a big issue with using genome editing for this kind of enhancement. Let's say for example, to improve your memory capacity or to improve for other people growth of muscles or enhance old people to have a stronger bone, for example. This is enhancement or is it already a therapeutic application? It's definitely preventative. So this kind of application, I think, should be possible" (H12).

Another scientist also saw enhancement as a potential positive form of HGE, but in this case because it is an ideal starting point for testing gene editing interventions, saying:

> "I'm astonished that the first things out that people talk about, when it comes to human genome editing, are going to be really important aspects of your health. Are you kidding me? What you want to do is something like eye color. What if it goes south and you come out with purple eyes instead of green eyes like you wanted? I mean, if you're adjusting pigment, it's unlikely it's going to do much else. But, wouldn't it actually be better if you wanted to start running tests on things that don't count? Hair color, whatever" (S13).

Prevention blurs the boundaries

Unlike the interviewees who challenged the normative distinctions between treatment and enhancement, many interviewees noted the conceptual difficulties of distinguishing between the categories. These interviewees interpreted TPE categories as identifying a spectrum of HGE uses. They maintained that clear instances of treatments and enhancements can be discerned at the extreme ends of this spectrum, but there are gray zones in the middle. For example, a governance group member commented:

> "I think it is possible to draw a line from definitional terms because there is a conceptual difference. But I don't think you can draw a sharp line in every case. So, there is kind of a continuum, but it is like between day and night. Is there a sharp line between day and night? No, not really. But, on the other side, we know that it is day here and tonight I will know, now it's night though I don't know whether there's a sharp line between day and night. So, there are the very clear cases with enhancements and therapy and prevention, and there are these gray zones, gray zone cases. But I think the distinction, that is my personal view, is nevertheless ethically relevant because it's something different whether you want to prevent a disease, which is a burden, which is causing harm and so on, or the wish to perfectionize, to optimize, to make something that is already normal, better" (G14).

This problem illustrates the emergence of prevention as a goal for HGE research, because, for these interviewees, it is in preventive uses that the gray zones emerge. Highlighting this phenomenon, one said, "It's hard to see where the line is between prevention and enhancement in some things like metabolism. So, if you shift your metabolism to be more stable, is that prevention of

diabetes or enhancement of metabolic function? So, it sort of leaps over a little bit into the next category" (H15). Another noted this leap, saying:

> "I think curing disease, I have no issue whatsoever, especially for incurable diseases. If somebody is gonna die and you can help them, then it makes a lot of sense. Disease prevention is a little more difficult because it's really a form of enhancement . . . I'm not . . .convinced about the disease prevention part very much. And the enhancement, at this particular time it's completely unethical. I mean, I think for us if we cross that line, then once you cross that line then there's no limit" (S16).

For this scientist, although treatment is sensible, the unethical nature of enhancement translates to questionable value for prevention because of the difficulty in disentangling the two categories. Another interviewee illustrated how prevention works as an intermediary between treatment and enhancement when describing a protective gene, *PCSK9*:

> "If my genes looked like the people with the mutant *PCSK9*, I'd probably have better cardiovascular outcome. So, by editing this gene, you're editing a healthy gene in healthy people to help them prevent a heart attack. That's different. Is that enhancement? I don't know. So, the definition of enhancement, I think people are often like, you know, oh, we'll have super soldiers, you can edit TGF-β and make them, you know, super musclely . . .. We shouldn't do it. But, I think that this question of what is enhancement, you can quickly get into some debate about what the definition is" (S17).

The gray areas, particularly around prevention, were also illustrated by comparisons with vaccination. An interviewee questioned, "Where are you gonna put prevention? Is that not all ultimately about enhancement? Is a vaccine ultimately not about enhancement, and how do you make those distinctions?" (G18). Expanding on this issue, another said:

> "I think the more interesting question is prevention and where does it fit in all of this. And obviously, the world is extremely focused on immune enhancement at the moment. What is vaccination but immune enhancement? And, no one is saying that's problematic in any way. We're trying to get as many people as possible to accept that. So, it's an interesting question. And obviously, for the purpose of preventing infections, it's long been a target, a goal, something that we think is an amazing public health success. But what I haven't thought much about, but is an interesting question, is when is that same kind of approach crossing the line. You know, it's not prevention, it's enhancement. So, you know super immunity? Interesting, . . . and what would that look like, a super robust immune system I guess for war fighting? I mean, I can think of all sorts of things that could be something that would be enticing to pursue, no more allergies, whatever. All sorts of things that you could imagine being advantageous or at least some people thinking worth trying to do" (G19).

Discussion

We have identified four themes that emerged from scientists' and governance group members' views on the distinctions between TPE. Some interviewees endorsed TPE distinctions to mark the limits of acceptable HGE, expressing their support for treatment uses and condemning enhancement. Others accepted these distinctions in principle but felt it was premature to attempt to define them in practice, primarily because it is unclear whether applications beyond the correction of simple pathogenic mutations would ever be possible. Some believed that the distinctions themselves and their usual normative interpretations simply depended on context, perspective, or the preanalytic values of those who would deploy them. Others, however, struggled to make sense of the distinctions, seeing a wide category of intermediate preventive interventions that confounded the distinctions. Each of these themes evokes various conceptions of and concerns regarding enhancement, some of which are represented in the bioethics literature, and different approaches to the governance of HGE.

The perspective that boundaries between treatment and enhancement are identifiable and meaningful conforms most with the traditional governance uses of the TPE distinctions, drawing a firm line between the legitimacy of treatment and enhancement applications.[1,2] The examples employed, such as designer babies, reflect the view that the problem with enhancement uses is that they apply genome editing technologies for goals that go beyond the treatment purposes for which the technologies were developed. Analogous to the problem of "off label" uses of pharmaceuticals prescribed for medical purposes, the problem here is using interventions developed to realize treatment goals beyond the boundaries of approved uses to achieve unrelated goals, raising the ethical questions that the enhancement category traditionally flags. The governance challenges raised by these kinds of "off label" enhancements are straightforward in principle, if not in practice. It requires the development and institutionalization of conventions that can prohibit or ban any use of HGE interventions beyond the boundary of medical applications. This governance approach was seemingly straightforward to these interviewees who, when explaining their views about enhancements, often expressed their opinion by supporting or calling for a ban. Notably, many interviewees described heritable interventions when advocating for a ban. Such a ban, for either somatic or germline interventions, would require "hard" national laws, professional policies, and international agreements policing off-label uses to establish control, akin to attempts to ban performance enhancing drugs in sport.

Those who thought that boundaries were largely irrelevant due to scientific limitations similarly acknowledged that the use of gene editing for enhancement purposes is a

theoretical problem. In fact, respondents with these views were also more likely to talk about heritable editing and largely pointed to the same traits viewed as enhancements as those who saw TPE boundaries as identifiable and meaningful (e.g., "intelligence, eye color, height, physique"), but took a different stance. Although those who see TPE boundaries as meaningful advocated for outright bans of these uses of gene editing, these interviewees view enhancements as currently too hypothetical to worry about, dismissing it as a practical concern because of the biological complexity of the traits involved and immature state of the scientific knowledge that would be required to target them. This view suggests that despite the popularity of such traits in philosophical discussions of the TPE distinctions, there is no good reason to try to address them until there is enough scientific evidence to make their anticipatory analysis worthwhile. As a result, anticipatory governance efforts are the purview of science fiction rather than science policy and, much like general worries about enhancement, are wasted time at best and unfair to achievable positive uses of HGE at worst. From this perspective, the only governance implications that the TPE distinctions raise is the need for continued governmental and philanthropic support to sustain the scientific research that can help assess the plausibility of those concerns and interventions seen as "hypothetical."

A third group argued that the boundaries between treatment and enhancement should not be normative for practice, a position that is also reflected in the bioethics literature.[9,15] These respondents focused on examples in which well accepted interventions are used to improve someone's traits beyond a baseline norm. Sometimes these enhancements occur at the individual level, as in the eye surgeries that compensate for poor vision by improving an individual's visual acuity beyond what they were born with. In other contexts, these "compensatory enhancements" boost traits beyond a population norm, as in some kinds of cosmetic surgery. Such interventions are generally acceptable by the medical community and the broader population, putting into question whether the boundary between treatment and enhancement should be invoked to inform regulation. If some enhancements are morally permissible, then additional values and principles must be invoked to distinguish between permissible and impermissible uses of HGE for enhancements. For example, policymakers should consider whether proposed uses of HGE threaten to give recipients an unfair advantage in a societal competition or may undermine relations of equality.[15,16]

Finally, while some thought the moral management of HGE enhancement would overlay already normalized forms of enhancement, many others found enhancement existed on a conceptual spectrum that is itself blurred. These individuals especially noted how preventive HGE aims introduce a conceptual gray zone. With this view, prevention raises issues both with respect to its acceptability as a goal of genome editing interventions and with respect to how we should understand the difference between it and enhancement as it introduces the prospect of interventions that bridge the traditional treatment/enhancement categories. This viewpoint from our interviewees echoes a longstanding ethical debate regarding the blurriness introduced by prevention.[8,17,18] HGE in healthy individuals, to give one possibility, might serve widely endorsed preventive goals by strengthening resistance to health problems in ways that create "incidental enhancements."[8] For example, efforts to prevent late life health problems by controlling cellular senescence might also extend the human life span beyond normal limits, a clear enhancement.[8] Another salient example of a potential incidental enhancement is how He Jiankui claimed his now infamous experiments on embryos to edit the CCR5 gene was meant to confer resistance to or "prevent" HIV infection in the babies later born. Nevertheless, in addition to the controversial initiation of rogue science human genome edits, he was quickly criticized by scientists and ethicists for performing enhancement.[19–21]

HGE governance documents tend to lump treatment and prevention together as acceptable HGE purposes,[3–5,22] although the European Group on Ethics in their Ethics of Genome Editing Report cautions against a standard use of these TPE categories without regular analysis of their meaning as prevention can blur into enhancement.[5] As our data reveal, the caution from the EGE is particularly important as these kinds of preventive goals present new complexity to the narrative in which treatment goals are generally laudatory and enhancement goals are ethically dubious. The distinctions here are not defined by the intentions of the user. Instead, they might occur as side effects or aftereffects of legitimate therapeutic or preventive interventions. They are essentially "secondary" to the original intent of the use, and governance issues emerge secondary to the natural sequelae of uncontested medical applications. Therefore, as with those who dispute the normative relevance of the boundary between treatment and enhancement, a case-by-case approach to governance would be needed. "Semi-soft" monitoring and review of protocols by scientific bodies like biosafety committees, IRBs, and funding review panels might work best, which would require professional, national, and international systems for the review and monitoring of individual protocols, along the lines of the UK's Human Fertilisation and Embryology Authority (HFEA).

Conclusions

Overall, the four themes that emerged from these interviews with primarily scientists and governance group members reflect significant differences on important issues such as how to understand enhancement and whether this is a useful category for governance restrictions on HGE. Three of the four themes reflect established positions in the bioethics literature, with the remaining theme challenging the central premise of this debate, namely, that enhancement applications are scientifically feasible in the near or even distant future. While some accepted the traditional understanding of the distinction between treatment and enhancement and rejected the latter as unacceptable, others argued that the concept of enhancement is largely irrelevant to discussions of HGE governance, and still others argued that enhancements are not as morally problematic as is often suggested. In addition, our data show how the seemingly benign addition of "prevention" as an extension of the reach of treatment uses of HGE in some governance documents may be more loaded than first appears to be the case. Rather than merely being an extension of the reach of treatment as intended, the addition of preventive goals creates a gray zone where respondents believed that prevention and enhancement goals may be difficult to distinguish. Depending on how they perceived enhancements, this could reflect negatively on preventive goals, call for a case-by-case analysis of the permissibility of HGE interventions, or simply offer one more reason to reject limitations on enhancements. The ethical and governance challenges of this intermediate category will be important to address as HGE research goals move beyond the treatment of serious disease to embrace longer range preventive goals.

Acknowledgments

The authors would like to thank those that participated in the interviews and the larger Incidental Enhancement team.

Authors' Contributions

M.W.: Conceptualization (equal), Formal Analysis (lead), Methodology (equal), Writing—original draft (equal); Writing—review and editing (lead); R.L.W.: Conceptualization (equal), Writing—original draft (supporting); Writing—review and editing (supporting); M.A.F.: Conceptualization (equal), Writing—original draft (supporting); Writing—review and editing (supporting); D.M.: Conceptualization (equal), Writing—original draft (supporting); Writing—review and editing (supporting); J.M.C.: Conceptualization (equal), Writing—original draft (supporting); Writing—review and editing (supporting); E.T.J.: Conceptualization (equal), Funding Acquisition (equal), Formal Analysis (supporting), Writing—original draft (equal); Writing—review and editing (supporting); R.J.C.: Conceptualization (equal), Funding Acquisition (equal), Methodology (equal), Formal Analysis (supporting), Writing—original draft (equal); Writing—review and editing (supporting).

Authors' Disclosure Statement

The authors have no conflicts of interest to disclose.

Funding Information

The work reported in this article was made possible with support from the National Human Genome Research Institute (1R01HG010661-01A1 R.J.C. and E.T.J., MPIs).

References

1. Anderson WF. Human gene therapy: Why draw a line? J Med Philos 1989;14(6):681–693; doi: 10.1093/jmp/14.6.681
2. Splicing life: A report on the social and ethical issues of genetic engineering with human beings. President's Commission for the Study of Ethical Problems in Medicine, Biomedical, Behavioral Research. The Commission: Washington, DC; 1982.
3. National Academies of Sciences, Engineering, and Medicine. Human genome editing: science, ethics, and governance. National Academies Press: Washington, DC; 2017 Jul 13.
4. WHO Expert Advisory Committee on Developing Global Standards for Governance and Oversight of Human Genome Editing. World Health Organization: Geneva; 2021.
5. European Group on Ethics in Science and New Technologies (EGE). Opinion on the ethics of gene editing. Publications Office of the European Union: Luxembourg; 2021.
6. Evans JH. The human gene editing debate. Oxford University Press: New York; 2020.
7. Nelson JP, Selin CL, Scott CT. Toward anticipatory governance of human genome editing: A critical review of scholarly governance discourse. J Responsible Innov 2021;8(3):382–420; doi: 10.1080/23299460.2021.1957579
8. Juengst ET, Henderson GE, Walker RL, et al. Is enhancement the price of prevention in human gene editing? Crispr J 2017;1(6):351–354; doi: 10.1089/crispr.2018.0040
9. Baylis F. Altered inheritance: CRISPR and the ethics of human genome editing. Harvard University Press: Cambridge MA; 2019.
10. Erler A. The limits of the treatment-enhancement distinction as a guide to public policy. Bioethics 2017;31(8):608–615; doi: 10.1111/bioe.12377
11. Pew Research Center. Public views of gene editing for babies depend on how it would be used. 2018. Available from: http://www.pewresearch.org/science/2018/07/26/public-views-of-gene-editing-for-babies-depend-on-how-it-would-be-used/ [Last accessed: Mar 14, 2024].
12. Pew Research Center. Americans are closely divided over editing a baby's genes to reduce serious risk of disease. 2022. Available from: https://www.pewresearch.org/internet/2022/03/17/americans-are-closely-divided-over-editing-a-babys-genes-to-reduce-serious-health-risk/ [Last accessed: Mar 14, 2024].
13. Patel K, Auton MF, Carter B, et al. Parallel-serial memoing: A novel approach to analyzing qualitative data. Qual Health Res 2016;26(13):1745–1752; doi: 10.1177/1049732315614579
14. Groenewald T. Memos and memoing. The SAGE encyclopedia of qualitative research methods. SAGE Publications: Thousand Oaks, CA; 2008.
15. Buchanan A, Brock DW, Daniels N, et al. From chance to choice: Genetics & justice. Cambridge University Press: New York; 2000.
16. MacKay D, Cadigan RJ, Juengst ET, et al. Egalitarian justice and the prevalence principle in human genome editing. Unpublished.
17. Fowler G, Juengst ET, Zimmerman BK. Germ-line gene therapy and the clinical ethos of medical genetics. Theor Med 1989;10(2):151–165.

18. Juengst ET. Can enhancement be distinguished from prevention in genetic medicine? J Med Philos 1997;22(2):125–142; doi: 10.1007/BF00539880
19. Greely HT. CRISPR'd babies: Human germline genome editing in the 'He Jiankui affair'. J Law Biosci 2019;6(1):111–183; doi: 10.1093/jlb/lsz010
20. Regalado A. China's CRISPR twins might have had their brains inadvertently enhanced. MIT Technology Review. 2019 Feb 21. Available from: https://www.technologyreview.com/2019/02/21/137309/the-crispr-twins-had-their-brains-altered/ [Last accessed: June 7, 2024].
21. Zhai X, Lei R, Qiu R. Lessons from the He Jiankui incident. Issues in Science and Technology 2019;XXXV(4):20–22.
22. Council of Europe. Convention for the protection of human rights and of the human being with regard to the application of biology and medicine. Hum Reprod 1997;12(9):2076–2080. Convention on Human Rights and Biomedicine or the Oviedo Convention (CETS n. 164); adopted in Oviedo on April 4.

Received: March 19, 2024
Accepted: June 21, 2024
Online Publication Date: July 8, 2024