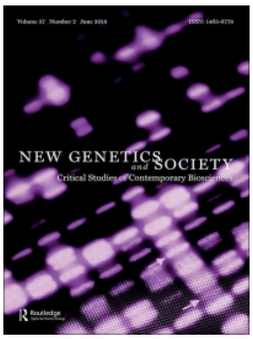

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Human heritable genome editing and its governance: views of scientists and governance professionals

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Heritable human genome editing has garnered significant attention in scholarly and lay media, yet questions remain about whether, when, and how heritable genome editing ought to proceed. Drawing on interviews with scientists who use genome editing in their research and professionals engaged in human genome editing governance efforts, we examine their views on the permissibility of heritable genome editing and the governance strategies they see as necessary and realistic. For both issues, we found divergent views from respondents. We place the views of these scientists and governance professionals within the context of the larger bioethical discussion of heritable genome editing governance, along a continuum of hard to soft approaches. These respondents' views highlight the challenges of various hard forms of governance and the potential virtues of soft governance approaches.

Keywords: heritable genome editing; governance; scientists; interviews; qualitative methods

Introduction

"Governance" has become a ubiquitous term in efforts to develop oversight for heritable human genome editing (HHGE) research, capturing the many ways, directions, and pace at which this scientific research could be controlled,

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limited, or standardized. The 2018 revelation of He Jiankui's experiments editing and implanting embryos to endeavor to confer resistance to HIV in the resulting babies catapulted global attention to the permissibility and governance of HHGE. The fallout included swift condemnation of He from the scientific community and calls for a moratorium of all such clinical research applications until "an international framework in which nations … voluntarily commit to not approve any use of clinical germline editing unless certain conditions are met" (Lander *et al*. 2019).

Governance includes but is not limited to government, in the sense of formal, "hard" legislation or regulation that can be enforced by government authorities. But scientific governance also takes numerous and diverse "soft" forms, like professional rules, norms, and practices; aspirational standard-setting by expert bodies and organizations; rules and practices of funding agencies; principles and practices of journal editors; and in the standards followed by universities in hiring, promotion, and tenure. Although soft governance mechanisms lack the binding force of traditional legal mechanisms, they often carry significant moral influence.[1]

Literature in science policy, law, and bioethics attempts to parse and weigh the relative virtues of different governance approaches to HHGE, including policy reports by influential organizations that aspire to a substantive role in governance (Adashi and Cohen 2016; Baylis *et al*. 2020; Brokowski 2018; National Academy of Medicine *et al*. 2020; WHO Expert Advisory Committee 2021). This literature echoes public concerns over the intrinsic merits, moral limits, and social permissibility of human genetic modification, and seeks to articulate governance mechanisms (including the proposed moratorium) that can address those concerns (Abuhammad, Khabour, and Alzoubi 2021; Armsby *et al*. 2019; Funk and Hefferon 2018; National Academy of Medicine *et al*. 2020; Normile 2023; Riggan, Sharp, and Allyse 2019; Rosemann *et al*. 2019; Scheufele *et al*. 2017; Segers 2023; Snure Beckman *et al*. 2019; The Lancet 2023). Some literature proceeds from the premise that HHGE research is inevitable and seeks to look ahead to questions of how it will mature as a practice rather than whether it should be embraced or rejected on categorical grounds (de Wert *et al*. 2018; National Academy of Medicine *et al*. 2020; Ormond *et al*. 2017). The Third International Summit on Human Genome Editing in 2023 concluded with a statement from the Organising Committee that declared HHGE "remains unacceptable at this time" because safety and efficacy have not been proven, public discussion and policy debates on the permissibility of HHGE are ongoing, and governance frameworks to ensure responsible use of the technology have not been instituted (The Royal Society 2023).

One central problem in seeking governance frameworks for HHGE is determining the relative ranking of the many possible oversight mechanisms. This task requires determining the extent to which different governance strategies can reflect ethical, social, and scientific concerns about HHGE research and the extent to which governance strategies pursue realistically achievable goals. Different lines of historical and sociological evidence are being marshaled in pursuit of these issues (Aikyo, Kogetsu,

and Kato 2023; Conley *et al*. 2020; Gregorowius, Biller-Andorno, and Deplazes-Zemp 2017; Mehlman, Conlon, and Pearlman 2023; Shozi *et al*. 2022; Townsend 2020; Yu *et al*. 2021), but important data sources relatively neglected thus far are the views of two groups who will be integral to the governance process for HHGE research: scientists who employ genome editing in research that might lay the groundwork for HHGE and members of governance groups whose work might be influential in formulating governance frameworks for HHGE. While individual members of these communities may have different views of the permissibility of HHGE and the feasibility of different governance approaches, both groups will have a major impact on the governance mechanisms that emerge because of their direct roles in the scientific evolution of HHGE. This influence extends beyond their local contexts to the global stage, given the international nature of the genome editing research community and the international focus of much of the governance groups' work.

This paper adds further empirical data on views of different HHGE governance regimes to inform the larger literature on genome editing governance (Nelson and Selin 2023; Ramos *et al*. 2023; Rosemann *et al*. 2019; Selin *et al*. 2023). Based on qualitative interviews with an international set of both scientists and HHGE governance group members, this paper addresses two questions: First, how do genome editing scientists and governance group members view the permissibility of HHGE? Second, as active participants in using HHGE technologies and/or assessing their use, what governance strategies are needed and realistic?

Methods

This study is part of a larger project on the ethical, legal, and social implications of the governance of human genome editing. Our study design included interviews with scientists whose research involves genome editing using non-human animals or human cells ("scientists") and individuals engaged in organized efforts to influence how human genome editing research should be governed ("governance group members"). We aimed to conduct 90 interviews, one-third with members of governance groups, with deliberate attention paid to recruiting an internationally diverse sample given the global nature of gene editing science and governance efforts. We chose 90 interviews as a goal with an eye toward saturation while still allowing for an inevitable diversity of viewpoints when speaking with professionals from around the world.

Eligible participants were identified through literature searches, conference presentations, and membership rosters of governance groups relevant to our project. Participants were recruited via email explaining the purpose of the study, the interview topics, and why we thought they could provide valuable perspectives. Participants provided verbal consent before the interview. Our study (#20-1330) was determined to be exempt by the University of North Carolina at Chapel Hill Institutional Review Board.

Semi-structured interviews were conducted from April 2021 through January 2023 via Zoom. They lasted approximately 60 minutes and covered topics including views on human somatic cell (non-heritable) and germline (heritable) editing and the governance of human genome editing (see Supplement 1). Respondents' views on the permissibility of HHGE emerged primarily in response to questions about what, if any, concerns they have about human genome editing applications and what distinctions they make between human genome editing interventions affecting somatic versus germline cells. Respondents were also asked how they thought human genome editing should be governed. Interviews were recorded and transcribed verbatim for analysis.

For the larger project, we used the Framework Method (Gale *et al*. 2013; Smith and Firth 2011), including an emphasis on analytic thematic memoing (Patel *et al*. 2016) to guide analyses of the interview data. To identify themes to facilitate analytic memoing, our team began with a deductive approach in which we created themes that followed from our research questions and interview guides. We then used an inductive, iterative approach to make additions or revisions to the themes by reading a subset of transcripts until we were satisfied as a team that we had appropriately captured and defined relevant themes of interest. For each transcript, we then summarized the relevant information for each memo theme and noted representative quotes and their context. The thematic memos permitted a systematic overview of what was contained within each transcript. We then created a matrix in Excel to organize our thematic summaries so that each row represented a different respondent and columns represented each theme.

For the results included in this paper, we first used the matrix to read through the memo themes of "Somatic vs. Germline," "Forms of Governance," "Scientific Self-Governance," and "Ethical Concerns" across all transcripts. We then used the qualitative data software MaxQDA to facilitate word searching across transcripts as an initial evaluation of the transcripts for our topics of interest (O'Kane, Smith, and Lerman 2021; Seale and Rivas 2012). We searched for terms that appeared frequently in our memos and the already identified quotes within the memo fields: herit; germ; embryo; govern; regulat; overs; ivf; and repro. We returned to the original transcripts where these words were used and read the surrounding text to ensure that we understood the context. This enabled us to get a sense of how the range of views were spoken about by interviewees before conducting a close reading of the transcripts (O'Kane, Smith, and Lerman 2021). We added relevant quotes on participants' views on permissibility and governance of HHGE to the matrix. If questions arose about the relevancy of quotes, we discussed them as a team.

Two authors (RJC and MAF) then conducted a close line-by-line reading and analysis of all transcripts (O'Kane, Smith, and Lerman 2021), taking further detailed notes on respondents' perspectives on HHGE and its governance, and ensuring familiarity with all the data and the breadth of perspectives. They also identified additional relevant quotes and added their notes and these quotes to

the matrix. They then documented patterns, connections, and variations across themes. Our team met repeatedly to discuss the views emerging from the data and their classification. Subsequent codes were created to facilitate analyses of our topics of interest for this manuscript – views on (1) permissibility of HHGE and (2) governance of HHGE. For example, we created codes for permissibility of HHGE that would later become the subsections we present in this paper (i.e. off-limits; hypothetical; permissible with safety guides).

Results

We conducted 92 interviews, meeting our goal of approximately one-third of interviewees being governance group members ($n = 33$) and the rest genome editing scientists not involved in governance efforts (Table 1). Some interviewees were both genome editing scientists and governance group members. Other governance group members were from diverse disciplines, including social sciences, bioethics, and law. Interviewees worked in regions around the world, with most in North America ($n = 38$) and Europe ($n = 33$). Most respondents were based in academic institutions ($n = 82$; 9 of these respondents were also involved in industry).

Results below are divided into two main sections: respondents' views and reasoning on the (1) permissibility of HHGE; and (2) governance of HHGE.

Views on the permissibility of HHGE

Approaches to whether and how HHGE should proceed fell largely within three lines of reasoning. First, there are no circumstances under which HHGE should be done – it is "off limits." Second, HHGE is still hypothetical in terms of real-

Table 1. Demographics of interviewees ($n = 92$).

	Variable	Frequency	Percentage
Interviewees	Scientist	59	64
	Governance Group Member – Scientist	22	24
	Governance Group Member – Other Background	11	12
Institution Type	Academic	73	79
	Industry	7	8
	Academic and Industry	9	10
	Other	3	3
Region	Africa	3	3
	Asia	9	10
	Europe	33	36
	Middle East	1	1
	North America	38	41
	Oceana	6	7
	South America	2	2

life applications, rendering the ethical questions largely within the realm of philosophy, not clinical application. And third, HHGE should be permissible when safety and efficacy are assured, with conditional requirements to guard against ethical violations. Responses were evenly split between the first and third categories, with those in the second category comprising a much smaller but still significant minority. There were no obvious differences in views between scientists (denoted as "S" when quoted), governance group members who were scientists ("GG-S"), and governance group members with other backgrounds ("GG-O").

HHGE is off limits

For a large portion of respondents, the prospect of HHGE was a scientific and ethical non-starter. One scientist stated forcefully: "What I am against is the germline gene editing or gene therapy. I think that this is not acceptable. The principle rule is that you avoid any germline gene editing or gene therapy" (Participant (P) 1, S). Another scientist also seemed to point to an agreed upon scientific maxim:

> [M]y first concern is really modifying [a] human embryo. I think that in the scientific community, we all agree that's something we should not do now, because you … not only change the genome of one person, but also of all his children later, so that's very problematic. (P2, S)

Other respondents also gave ethics- or principle-based reasoning for prohibiting HHGE, such as concerns about eugenics; the possible effects on future generations and the larger human gene pool; and the right of the future child to have not been genetically modified. A scientist and governance group member pointed to consent, commenting, "[T]he recipient is not in a position to understand or give consent and it's being done to them, which I think is ethically, no" (P3, GG-S). One scientist used spiritual beliefs as well as their desire to help people who currently have disease (rather than preventing disease by editing embryos) to reinforce that HHGE should be impermissible:

> As a scientist, I want to develop medicine to help people. And mostly, when I say help people, that there are people already suffering from disease. I still believe, whether you call it God or a higher power, … people cannot cross that line to create … that kind of human being. I think that's dangerous. (P4, S)

For others, HHGE was problematic for both technical and humanistic reasons. One scientist commented, "I think, safety-wise, it is better not to touch germlines. Ethically, it's better not to touch germlines" (P5, S). When respondents pointed to safety concerns to justify their view that HHGE should not be done, the terms they used often expressed moral judgement, like a scientist who called HHGE "highly irresponsible":

> If you change one nucleotide out of three billion, you statistically cannot be sure not to change something else. This is just pure statistics. And there are very few safeguards. You can sequence the DNA in an embryo before you put a group of

> embryos back into a pregnant woman and things like this. Yes, you can do a lot of things. But I think it's highly irresponsible. (P6, S)

Similarly, another scientist called HHGE a "blundering intervention" that "we should forbid." When referencing their experience with non-human animal embryo editing to emphasize the technical limitations that should prohibit germline editing in humans, they said:

> [W]e are not yet able to direct and really know what changes we are going to generate in this new embryo … because we do that extensively in animals, we know this is a very hit-and-miss system. And the consequences are often many embryos which are not viable, or which have a poor outcome in terms of development. There's just a few very precious embryos which are what we hoped they should be … . So for me, that level of blundering intervention makes it so we should forbid ourselves to go for a germline intervention. (P7, S)

Beyond safety concerns, other scientists argued that HHGE is not medically necessary because there are "lots of other options before you get to that final trigger," even for families seeking to avoid passing on a genetic disease to their children (P8, S). One explained:

> If you have a genetic disease, for example, you can have children with other options. If you [have] a mutation, you can, for example, generate embryos in vitro and then select those that don't have the mutation. (P9, S)

HHGE is largely hypothetical

For a relatively smaller group of respondents, HHGE was seen as largely hypothetical. They were skeptical about its readiness and the demand for it, but they did not say it should be impermissible as respondents with the "off limits" view argued. Instead, the question of circumstances under which HHGE would be acceptable was simply moot. The technology is "not ready," as one scientist and governance group member (P10, GG-S) said, and safety concerns may never be overcome. Like some with the "off limits" view, these respondents also pointed to the lack of medical necessity for such treatments, noting that safer, more practical options already exist for many patients who might consider HHGE, such as preimplantation genetic diagnosis (PGD) or mitochondrial replacement therapy (MRT) (aka "three parent babies") used with in vitro fertilization (IVF).

This group also noted that HHGE is largely hypothetical because of the market forces playing a role in whether HHGE moves forward. One scientist and governance group member commented on low consumer demand for HHGE, saying, "The issue with heritable is very much in the future. It's not something that we are actively thinking about, and it's not something that patients ask for. [They] ask for treatment … , but not really [for] going into the germline" (P11, GG-S). Respondents noted that this low consumer demand, coupled with scientific limitations, safety, access, and cost mean that industry will not be interested in pursuing

HHGE. As one scientist commented: "Having been part of meetings at all different kinds of policy forums, I think it's safe to say that no biotech in the US is either allowed or even remotely contemplating germline editing" (P12, S). A governance group member remarked, "[T]he number of people who really need it and really want it is still going to be so small that it's not likely to put enough pressure on anybody to try to offer up the service." (P13, GG-O) Similarly, a scientist and governance group member wondered why substantial time and energy should be devoted to creating international guidelines, commenting, "We are focusing on an issue which doesn't have that big of a practical impact," adding "because there's not going to be many people doing human germline editing" (P14, GG-S). What these respondents saw as lack of demand and utility meant that, at least for now, HHGE has little clinical potential.

HHGE should proceed with safety guides

The third category of respondents, similar in large size to the first category, sanctioned moving forward with HHGE within specific parameters. As one scientist and governance group member argued, there are "circumstances where it's entirely justifiable, if done safely, of course" (P15, GG-S). For this respondent, it seemed imprudent to question the use of HHGE across the board, explaining: "The question, 'Heritable human genome editing: yes or no?', it's a really silly question. It should always be, 'In what set of circumstances might HHGE be justifiable?'"

For these respondents, settling on the ethically acceptable circumstances or boundaries for HHGE is paramount, as were the parameters within which responsible progress could move forward. A governance group member specified, "I am totally enthusiastic about heritable human genome modification for serious fatal diseases, so that these diseases can be eradicated" (P16, GG-O). Other respondents approved of using HHGE to address serious or fatal diseases, but identified additional questions raised by this view. One such scientist and governance group member asked, "But for what disease?" suggesting there could be a list of acceptable diseases (P17, GG-S). Another offered a conditional recipe for moving forward:

> We are not yet there. But as soon as we are close to being there, we need to begin to fix a number of conditions. … So, it must be a pressing disease. It must be a very severe disease … you must have tried all of the different alternatives and failed. You should have validated this at the preclinical level, the mutations that you plan to correct with the given sequences. The sequences you plan to introduce should be the ones [that] commonly present in the human genome, etcetera. (P18, GG-S)

Overall, this group of respondents saw little reason why HHGE applications cannot be used once safety requirements are met. The concerns that informed the "off limits" view that heritable editing should never be used took a backseat for this group to the ability to stop disease inheritance. One scientist argued:

> You consider that patients that have an inherited disease, why should they not have the right to cure their next generation, cure their offspring? This is a discussion that needs to be open. [T]hey also have the right to be cured when there is a cure for them, so that they don't have to be afraid that every one of their children is going to be 'as sick as I am.' It's possible. (P19, S)

This respondent continued, expressing another point shared by others: HHGE is not a matter of permissibility because it is inevitable. He noted,

> You cannot control what happens in whatever lab anywhere in the world. So, it's not a discussion to allow or not to allow it because it's easy, it's accessible, everybody can basically do it. It's not rocket science anymore, so a futile discussion at this point. (P19, S)

Similarly pointing to the inevitability and potential uncontrollability of HHGE, a scientist and governance group member said:

> Look, if some guy in Russia wants to do something, some guy in Russia is going to do something. I think we all learned that with He Jiankui, you know. I mean, it's not so much of a problem … . If a nuclear reactor leaks, it's a problem for other countries. If … one of their citizens opts into a trial, I don't think that's a problem for us … . If someone in Russia or China wants to do this, I don't think it's my business, really. (P20, GG-S)

Respondents in this group sometimes used the same justifications for moving forward with HHGE that others used for prohibiting it: namely, the application to only a handful of diseases that affect a limited number of people. As a scientist said:

> So, there's a clear case made for some diseases – very early onset and lethal diseases, then yeah, germline application is justified. Also, because these diseases are very rare, with this you would not do some massive blunder population-wide where suddenly five years down the line when conditions change, we have five million people drop dead. It's a very limited number of patients that would be affected by this, so it would not change the population at large. (P21, S)

In contrast with the other two camps, though, some respondents in this category saw this technology as having generational benefits, framing the permanent changes to the genome in a positive light, even as ethically preferable to somatic cell editing done on a single individual. For instance, a scientist and governance group member argued:

> If you were to fix someone of their cystic fibrosis or their sickle cell disease or something like that, as an embryo, then that means they also do not carry that gene on into the next generation. So, there's actually some ethical weight behind [HHGE] being preferred. If you're going to do good, if you're going to do something, then the amount of good that you do is even more so if you not only help that person, but you've helped every generation beyond that person. (P22, GG-S)

Views on governance of HHGE

Below we offer various perspectives on HHGE governance that emerged in our interviews, including both the ideal and necessary types of governance, significant barriers to global governance, and suggestions for how HHGE governance might proceed.

Governance should be global

A large portion of respondents who offered views on HHGE governance models discussed the necessity of establishing globally recognized boundaries for the use of HHGE, describing the importance of international "coordination," "consensus," "dialogue," "umbrella paradigms," and "guidance." A scientist and governance member commented, "We need more international governance frameworks and binding legal structures, which we don't have yet … " (P23, GG-S). Other respondents pointed to existing guidelines that might delineate permissible versus non-permissible uses of HHGE (e.g. National Academy of Medicine *et al*. 2020; WHO Expert Advisory Committee 2021) and hoped they would have global impact. The Oviedo Convention was suggested as a possible model of international governance that offers guidance but permits flexibility among nations (Council of Europe 1997). One scientist and governance member commented, "There are some countries that have signed the Oviedo Convention and say genome editing in the germline should be prohibited, and others have not" (P17, GG-S). They continued:

> The European Union is a quite diverse union with countries of very different, let's say, societal backgrounds. And, for some of the regulations we have this subsidiary principle that is a common rule, but the countries are allowed to act by themselves within a certain framework. And this, I think, could work for an international treaty. (P17, GG-S)

Others were similarly concerned about flexibility among nations but called for a new international advisory body to monitor the science of HHGE to advise on what is safe so that jurisdictions could enact their own regulations.

For some respondents, international governance, in whatever form, was an important way to prevent "rogue" nations, "medical tourism" or research "forum shopping." A scientist commented:

> [S]cience is quite international at the moment still, so I would opt for that it should be kind of a consensus worldwide so all the regulations would be more or less the same in different countries. … [T]his would also be good for the patients because if we have the same regulations, then the people won't move from one country to the other just because in one country this is allowed and in the other one it's not. (P24, S)

Some who cautioned against medical tourism and forum shopping pointed to the 2016 case of the first MRT, or "three parent babies." In that case, a US physician,

John Zhang, traveled to Mexico to implant an embryo created using MRT in a Jordanian couple who had two prior children die of Leigh Syndrome (Reardon 2016; Zhang *et al*. 2017). Others who noted concerns about "rogue" scientific uses conjured, explicitly or implicitly, He Jiankui's editing embryo experiments in China, which resulted in at least two live births. Respondents used this case to argue the importance of an international governance mechanism. As one scientist and governance group member said:

> The trouble is, if the Chinese – any country, I shouldn't say the Chinese – if any country chooses to do this, that's the camel's nose under the edge of the tent … It's like it's the beginning of the end for regulation because what's okay here, well, let's do it a little more. So, I think there's a need, at a very high level, for this to be addressed at the international level. (P25, GG-S)

Another scientist and governance group member offered:

> Some researchers in some countries are very bad clinicians if they try to do HHGE. So, how can we stop or how can we find out [about them] at an earlier stage? You need some system of governance at the international level. (P26, GG-S)

Global governance has significant barriers and limitations

While respondents advocated for international governance in a variety of hard and soft forms, most simultaneously talked about significant barriers and limitations to implementation and enforcement. For example, a scientist and governance group member noted:

> It's a difficult area, of course, to decide how this should be done because there is no very good precedent. There is no international jurisdiction. But I think something will follow definitely, and that should be international. But who will organize it and how, and who will be involved? I don't know. (P11, GG-S)

Another commented about the complications and limitations of enacting hard governance on a global level:

> [T]here are no international laws. The only thing we have is national laws, and there are people that do not understand this. We have national laws, and then we have treaties, declarations, recommendations that are normally not mandatory, that are accepted on a willing basis. (P18, GG-S)

Given the lack of international law, some interviewees questioned the effectiveness and practical enforcement of international governance. One such scientist drew a parallel to existing international governance bodies, arguing that the WHO and United Nations lack the power to enforce. Similarly, a scientist and governance group member commented:

> What came out of [the WHO Report] at the end is something which probably will not work, as most things don't, because when I think of regulations of various kinds, … [they] only work to the extent that local authorities are interested in enforcing

> anything. And, I don't know to what extent anyone … is interested in enforcing CRISPR regulation. (P27, GG-S)

For another scientist, the patchwork of global governance enforcement called for a stronger warning, claiming, "We're heading for something, for a train wreck. But you can't get any sort of international consensus that's actionable" (P28, S). Another cautioned that gene editing is "like any other technology. Once you have, you use it, and somebody is going to use it no matter what the regulations are. Or, some country is going to say, well, we're not going to follow those regulations" (P29, S). For these respondents, without accountability and enforceability, any attempts to govern internationally fall flat.

Other respondents expressed concern that efforts toward international governance might exacerbate inequalities between nations: more powerful countries would develop governance based on their own interests, preferences, and cultural norms, which would not reflect those of less powerful countries or groups. One scientist, for example, hoped that there could be international consensus on "the most extreme" issues around HHGE, but cautioned that "every country has a different set of priorities, and you cannot shove your priorities down their system" (P30, S). Another advised, "There has to be representation in international decision making … . So, it cannot be a … very polarized opinion from a few countries, but rather have a very balanced opinion from a very large number of countries" (P31, S).

To this point, some interviewees saw parallels between governance for HHGE and current governance of similar reproductive technologies like PGD, IVF, and MRT. For example, respondents discussed how the permissibility of PGD itself, as well as which diagnostic tests are performed, is not the same across countries, and in some places has little to no regulation:

> They can't do PGD in Germany. Germany has very strict rules around this because they feel like the world is looking even closer at them because they're like, 'Bad things happened here, we promise we're not going to do anything bad again.' … Other places, you know, in America it's like you can buy what you want. You can do sex selection if you want. In the UK, sex selection is illegal. So, we don't even have rules that cross the world of assisted reproduction. (P32, S)

A governance group member viewed IVF's varying regulations both within and between countries as evidence that global HHGE governance is not possible, nor desirable. Discussing the variance between states within the United States, this interviewee cautions that barriers to international governance are insurmountable:

> If we can't do it on a national level only with IVF, how are we ever going to do [HHGE] on a global level? I think it's impossible, it's a dream. It's a utopia to think that we would be able to do that. And it would be undemocratic in many ways … because of the diversity of our cultures, the diversity of our mind sets, our world views. (P16, GG-O)

Governance can be national

Respondents offered ideas on how governance for HHGE might proceed outside of international governance by borrowing from existing national governance models. Some pointed to the United Kingdom's Human Fertilisation and Embryology Authority (HFEA), which regulates fertility treatment and human embryo research. The HFEA was seen, particularly by UK respondents, as a model to emulate in other parts of the world for monitoring the science regarding the safety of HHGE and advancing regulation. Respondents commented that the HFEA is "proper regulation" (P33, GG-S) and appreciated that the HFEA was legislated by the UK government but works independently. Some noted that the HFEA is skilled at convening public consultations around emerging technologies and could do the same for HHGE. These respondents specifically pointed to the recent legalization of MRT in the UK following public consultation. One scientist and governance member, when describing a model for HHGE governance, commented:

> I think the HFEA is a good way to go. I think the HFEA will probably lead some of the discussions about these new technologies such as genome editing. It certainly did with mitochondrial replacement. It organized public-facing events and deliberate discussions. I can imagine them doing the same with heritable genome editing. (P15, GG-S)

Other respondents advised that national medical boards could hold heavy influence over clinical applications of HHGE, although they acknowledged that their influence varies country to country. For example:

> The National Academies came out with their statement on genome editing. It doesn't help unless the medical control boards within all the countries agree to the same approach. And that, of course, is basically a treaty … . In most countries outside the US, because of the national health service and the controls over medical practice, you could impose that quite easily. I say 'except for the US' because you don't have a nationalized … medical system … So, that creates a problem. Can we define the conditions by which most countries would agree that this technology can only be used in certain circumstances? I think the answer is yes. (P34, GG-S)

Anticipatory, flexible governance

Regardless of whether governance is international or national, some respondents advocated for jurisdictions to employ anticipatory governance, suggesting that governments gather scientists to look at the current state of the technology and anticipate problems: "[I]f we can envision what is going to happen, good direction and bad direction, and then try to come up with either regulation or any way to prevent that people misuse the technology, I think that would be great" (P4, S). A governance group member similarly commented:

> I'm the kind of person that feels that if we keep our eyes open and we have a grip on regulation, that we are able to move along with the science, we will be able to adapt law to the science as it grows exponentially, which I think it is. (P16, GG-O)

Like anticipating the directions of a technology, some respondents advocated for flexibility, saying that regulation:

> [N]eeds to have a fine balance between overacting and being too loose … . I mean, it really needs to be readjusted every once in a while. It cannot be rigid because we are proceeding so quickly with our developments that also the regulatory authorities need to adjust to the new situation and then say, 'Okay, we can deregulate this, we have to be more regulative here, we have to be more careful there.' … We need development and we need safety. (P19, S)

Some respondents were concerned that regulations would always be behind the science. One scientist called for regulations that do not target a specific technology like HHGE but rather target ethical questions and then apply to similar technologies:

> I think there is an opportunity to think about new technologies per se and not isolate each one of them and create specific regulations for each one of them because there should be a scientifically reasonable approach to things. It doesn't matter what tools you are using. We need to look at what they're used for and what [are] the questions we want to be answered when the technology is being used. So, if you base the policy on questions, the technology still doesn't matter, and it will enable the development of new technologies and applications of new technologies because, fundamentally, the questions are not going to change. (P35, S)

This idea was echoed by a scientist and governance group member who remarked that their governance group had many discussions about "What is specific to genome editing? … [W]hat is genome editing reviving as issues, or maybe reopening or giving the opportunity to reopen domains that have been discussed previously?" (P36, GG-S).

Soft governance

Respondents suggested various forms of soft governance – described as "social regulation" by one scientist (P37, S) – to help guide if and when HHGE is used. Whether respondents advocated for primarily international or national level governance, soft forms of governance were seen by many as integral to practical enforcement; some appealed for a combination of hard and soft governance. A scientist remarked, "Mechanisms in which scientists monitor themselves will not suffice. This is because there are no criminal penalties for non-compliance. State involvement is required. I think an international code of ethics and oversight framework should also be created" (P38, S). Likewise, a governance group respondent suggested:

> If you have an idea about what you want for the direction of a technology, it makes sense to look at all the governmental and non-governmental forces that are driving it in whatever direction and ask, 'Do I want to nudge it in a different direction, and which of these entities has that power and which tool can I use to leverage them?' (P39, GG-O)

Even if countries do not set their own regulations regarding HHGE, soft governance could have wide impact. For example, a scientist and governance group member hoped that existing international organizations might be able to provide enough sway to influence the adoption of certain standards related to HHGE:

> Nobody will be able to force the Chinese government or the Russian government to adopt some law if they don't want. So, it's the global idea of self-law: that, if sufficient authority like UNESCO IBC [International Bioethics Committee] or like WHO Science Division or Science Council are setting standards, it will infuse as self-law the regulatory reform. And those who want to play the game will adopt these standards. So, it's clearly wishful thinking, but considering what already failed, we can try this one. (P40, GG-S)

Another scientist and governance group member said regulating human gene editing research should have "layers" of hard and soft mechanisms:

> I think there's many layers to this, but … there's probably a role for the legal apparatus of, you know, states, countries, and internationally to forbid particular types of interventions and have limits to what we do. I also think there's kind of the soft self-regulation that scientific societies have and that professional associations have. And then, institutions, as well, have their own set of policies and oversight mechanisms. (P41, GG-S)

Several respondents noted the important role journal editors play in soft governance because scientists are incentivized to publish. One scientist remarked:

> If you perform your study, you have to publish it. And there [are] already ethical guidelines from a general level – this is a study [that] involves human subjects or human embryos or human cells. Is that in line? So, these are … governance. There's [an] environment [of] governance around. (P42, S)

Likewise, others argued that those who grant patents can serve a similar soft governance role.

A handful of respondents mentioned the idea of a global reporting system (e.g. WHO Expert Advisory Committee 2021). This notion arose from the revelation that people knew He Jiankui was planning HHGE experiments, but there was no mechanism to report him.

Others voiced concern that a reporting mechanism may not have prevented He Jiankui's experiments, and one scientist and governance group member offered an alternative to a reporting mechanism in the form of peer pressure:

> Scientists depend on the respect from their peer group. So, they will always be interviewed, present at meetings, you'll do things internationally. And I think if there's more transparency about what's going on in every country, then you're never going to eliminate the rogue scientist, but you will at least reduce the likelihood of the rogue scientist operating without anyone else knowing. (P43, GG-S)

Discussion

Our investigation of scientists' and governance group members' views on the permissibility of HHGE and its governance highlights the difficulty of creating forms of governance that address the ethical, legal, and social complexities of HHGE. Our findings have limitations. Although we made efforts to recruit a global sample, most respondents were in North America and Europe, and only a few respondents were from low- and middle-income countries. We also only conducted interviews in English, which limited our geographic representation of respondents. While we asked respondents about their views on human genome editing and its governance, we did not ask about how their specific work context (e.g. scientist in academia or industry, scientist who is also a governance group member, governance group member from non-genome editing scientific discipline) relates to their views on HHGE and governance. However, our interviews provide rich descriptive detail and offer a range of views of both the permissibility of HHGE and its governance and bring to light problems in governance efforts that may help in addressing them in full.

Overall, perspectives on permissibility fell within three categories: HHGE is impermissible in all circumstances; permissibility is moot since HHGE is still hypothetical in terms of real-life applications; and HHGE should be permissible when safety can be assured, with additional requirements to guard against ethical violations. The category of HHGE-as-hypothetical was small relative to the other two categories (impermissible and conditionally permissible), which had similar numbers of supporters among our respondents. The amount of support for moving forward with HHGE is surprising given the calls for moratoria that followed He Jiankui's experiments (Alsomali and Hussein 2021; Lander *et al*. 2019; Martin and Turkmendag 2021). Few respondents endorsed a full-speed-ahead approach, with nearly all supporters wanting conditions of safety and efficacy that many acknowledged might not be achievable, but this "in principle" support gives license to researchers to proceed with addressing the scientific challenges in ways that a categorical negative response on ethical or philosophical grounds would prohibit.

The overall lack of consensus among our respondents on the underlying questions of whether and how HHGE should proceed highlights the conflicting value systems that complicate the development of governance mechanisms. Importantly, this absence of shared norms demonstrates not just the complexity of governance of HHGE, but also the need for it. Our findings illustrate how governance options for HHGE are arrayed from "hard" (comprising laws and regulations enforceable by governments) to "soft" (numerous mechanisms that are more informal, flexible, and non-binding, but likely hold moral weight to influence behavior or cooperation, such as professional guidelines and best practices), and that the two likely work best in tandem.

Respondents' views on hard, international HHGE governance reflected both aspiration and skepticism. Respondents with aspirational goals for international governance tended to frame HHGE as a case study of how science should be conducted in our globalized world. These respondents' goal is a soft governance "transnational professionalism" based on universally agreed upon principles (Faulconbridge and Muzio 2012; Yu *et al*. 2021). Some supported the view that this transnational professionalism can be sufficient to manage risk, eliminating the need for new regulations. In this view, HHGE is seen as an unexceptional technology, which might allow it to fall under existing frameworks like the Oviedo Convention (Council of Europe 1997). For others, aspiration was tempered by apprehension, driven by the belief that HHGE *is* exceptional in its possible impact on future generations, differentiating it from established applications and necessitating specialized guidelines and regulations. Regardless of their level of apprehension, respondents expressing aspirational views saw a pathway for HHGE, either by building on existing global frameworks or by creating new ones.

However, as the multiple respondents who were skeptical about international governance emphasized, achieving governance that is both global and "hard" is extremely difficult. The process would require all relevant countries agreeing to a treaty, then translating its elements into national law, and then abiding by it. The Paris Climate Agreement, for example, though nominally adopted by 196 countries in 2015 (United Nations Framework 2015), has foundered in part because the US never took the ratification steps necessary to translate it into national law and because many signatory countries have ignored their obligations. The Oviedo Convention, seen as a possible framework by some, has similar issues, having never been ratified by such major biomedical research powers as the US, Germany, Japan, and the UK. For HHGE, the interest in adopting and enforcing regulations will vary dramatically between countries; many countries may see regulating HHGE as a low priority compared to other needs of their citizens.

Even if we were able to achieve a global governance regime, enforcement across borders becomes complex when national interests diverge. Aligning with previous studies, our respondents noted concerns about rogue nations, sometimes discussed in terms of "medical tourism" or "forum shopping": some countries may decide to allow or encourage HHGE that would be forbidden elsewhere (Chan and Medina Arellano 2016; Rosemann *et al*. 2019). Another issue for global governance is that technological breakthroughs like HHGE often race ahead of regulatory frameworks. Governance must adapt swiftly, and adapting any global standards to emerging breakthroughs would require ongoing work. Flexibility without compromising safety is crucial. Hence, as some respondents and others in the literature have argued, readily adaptable anticipatory governance may be critical (NASEM 2017; Nelson, Selin, and Scott 2021; Nestor and Wilson 2022; Nuffield Council on Bioethics 2018; Selin *et al*. 2023; Zhang *et al*. 2022).

While national-level governance may be easier to achieve, it is not without its challenges. Licensed physicians working on clinical applications of HHGE might be subject to state-backed professional discipline by national medical boards, but boards' influence over clinicians varies dramatically, as both respondents and others have noted (de Vries *et al*. 2009). In addition, national medical boards would not cover the research realm of HHGE, necessitating additional forms of governance. Some favored modeling national regulations on those of similar technologies like MRT and PGD in IVF. However, as respondents noted, major international differences in regulating these technologies already challenge reproductive equity and access. Some respondents suggested following the specific model of the UK's HFEA, the independent regulator of fertility-related treatment and research using human embryos that regulates through a combination of hard and soft governance – granting licenses, conducting inspections, and setting standards.

With respect to softer forms of governance, the consensus recommendations issued by elite groups like the WHO Expert Committee and the International Commission are purely advisory (National Academy of Medicine *et al*. 2020; WHO Expert Advisory Committee 2021), but nonetheless difficult for anyone in the HHGE field to ignore for at least two reasons. First, because of the prestige they carry, these recommendations are likely to be embodied in any specialized laws and regulations that governments enact. Thus, even in the absence of enforceable international law, any new national laws (and interpretations of existing laws) are likely to converge on the principles recommended by these elite groups. Second, these groups notably include influential genome-editing scientists, meaning that governance group recommendations are coming, at least in part, from scientific peers. These recommendations thus have a recursive quality, expressing and reinforcing shared values within the scientific community. Consequently, though nominally soft, the recommendations are likely to exert real power over HHGE practice at every level.

Multiple participants expressed skepticism about the still-softer option of scientific self-monitoring because enforcement of norms lacks state backing. This skepticism is certainly warranted. However, some soft enforcement mechanisms – denial of funding, tenure, or publication, for example – may have sharp teeth indeed for many affected parties, even if they lack the authority of government. Yet such soft governance sanctions alone are not likely to entirely deter "rogue" scientists. He Jiankui's dangerous experiments, and the professed knowledge of them by other professionals, represent a governance failure that cannot be ignored, and responses invoked both soft and hard forms of governance (the Chinese government imprisoned him for three years). Since He's experimentation is – so far – unique, there is still reason to believe that soft governance mechanisms hold influence in deterring similar misconduct, particularly if paired with harder governance mechanisms.

Conclusion

Our results illuminate the various challenges of creating governance for a globally available technology that has no consensus for its eventual permissibility. Hard global governance of HHGE may be unrealizable, and national governments may struggle to keep up with rapid scientific change. Softer governance mechanisms clearly have an important role to play in enforcing ethical behavior. But they should not be relied on to do the job alone, and instead should be part of a broader mosaic of governance strategies. While hard regulations may lag behind both scientific change and the soft governance mechanisms that evolve in response to such change, their enactment can be important as authoritative statements of prevailing norms. As has been seen with other technologies, diverse governance mechanisms can and often do reinforce each other. Soft governance can reflect evolving values, and while norms may be soft in the abstract, they can take on a harder edge when embedded in, and constantly reinforced by, a network of practices that have real-world conventions and hard constraints.

Note

1. We use the term "soft governance" instead of "soft law" to avoid confusion and underscore that soft forms of governance are different from legal regulation.

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Data availability statement

The data that support the findings of this study are available upon reasonable request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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