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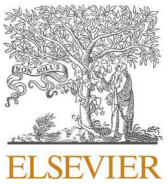

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Seven open questions in the futures of human genome editing

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ABSTRACT

Scholarly discussion around the governance of human genome editing (HGE) recognizes that development and application of HGE techniques could result in unexpected societal outcomes. However, it contains few to no methodological models for how to anticipate, prepare for, or shape such outcomes. This article presents early-stage results from research guided by anticipatory governance, a framework for broad expert and public consideration of innovation processes and purposes. We present and discuss key themes emerging from a set of future-oriented interviews with genome editing practitioners and experts, designed to inform broadly scoped deliberations about plausible futures of HGE. We articulate our results as seven "open questions," the answers to which will be important components of HGE's eventual shape and outcomes. Some themes are perennial in studies of science and society, and others are more novel to HGE. Each helps to reframe HGE beyond a simple comparison of risk and benefit. Such reframing opens up new and important terrain for discussion among policymakers, academics, scientists, and publics. We suggest that discussion framed around broad and reflexive questions like those presented here will help governance efforts to better acknowledge and flexibly respond to the uncertainty and complexities of HGE developments.

1. Introduction

In late November 2018, the scientific world was caught flat-footed by reports (Regalado, 2018; Marchione, 2018a) that U.S.-trained biophysicist He Jiankui had at the embryonic stage performed heritable modifications on the genomes of two (then-)recently-born baby girls. Prominent researchers quickly labeled He's actions a "deeply disturbing" violation of "international norms" (Baltimore et al., 2018) and "a failure of self-regulation by the scientific community" (Marchione, 2018b). The discovery came on the eve of the Second International Summit on Human Genome Editing, where He himself was scheduled to speak. Summit organizers, many of whom were globally prominent genome editing researchers, decried He's actions onstage and offstage, declaring that it had been irresponsible of him and would be irresponsible for anyone else to bring modified human embryos to term. Roughly 24 h later, the same organizers professed that it is necessary to "define a rigorous, responsible translational pathway" (Baltimore et al., 2018) toward doing exactly that.

The 'He debacle' was most dramatic spur in worldwide research, bioethics, and policy communities' ongoing scramble to come to grips with the prospect of human genome editing (HGE). This discussion has included numerous prominent calls for forward-looking

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governance of HGE (e.g. National Academy of Sciences and National Academy of Medicine, 2017; Nuffield Council on Bioethics, 2016, 2018). The very urgency of these calls, however, raises several questions. Why was there little movement for forward-looking governance before HGE became feasible? Why were scientific and governance communities seemingly unprepared for He Jiankui's work? What forms of foresight might have permitted researchers, policymakers, and publics to prepare for the possibility of HGE before CRISPR-cas9-based techniques made it so easy that some (e.g. Church, 2015; Doudna, 2015; Juengst, 2017) now see such surprises as inevitable?

This manuscript offers some suggestive answers to these questions, arguing that human genome editing was able to leap as fait accompli upon an unprepared world largely because institutionalized modes of science governance and foresight systematically disregard long-term, uncertain, and unquantifiable outcomes of research and innovation. Science governance in practice still reifies the much-derided linear model of innovation. Mainstream governance discourse takes technical change as unpredictable, inevitable, and universally beneficial, thus free of the possibility or need for anticipation or control. What little foresight occurs focuses on near-term, quantifiable, individual risks to the exclusion of longer-term, more diffuse, less certain, but more important impacts. Section 2 expands upon this argument through a brief summary of past and present discussions of HGE governance.

Following this discussion, we illustrate potential alternatives to the constrained risk-benefit discourses that failed to anticipate He Jiankui, building on scenario methodologies to reframe the sorts of possibilities meriting consideration and address in sociotechnical change. We articulate alternative frames of consideration based upon in-depth qualitative interviews with a multidisciplinary group of 30 experts dealing with HGE governance. Each theme moves beyond clear-cut cost/benefit, risk/opportunity, should/ should not prognoses, and rather explores sites of contestation that can be expected to shape the future of HGE. These formulations aim to draw attention to the indeterminate and plastic nature of many of the aspects of HGE most relevant to its eventual societal outcomes. Section 3 describes the methodological approach to interviews and analyses that enables such reframing and provide one way through the thicket of complexities and uncertainties of socio-technical change. Section 4 presents seven themes identifying core uncertainties about the future of HGE, supplemented by parallels in prior scholarship and illustrative quotes from interviewees. Section 5 articulates the import and utility of such questions for a more empowered governance of HGE.

2. Background: mainstream HGE governance and responsible innovation

2.1. Unthinkable until unavoidable: dominant sociotechnical frames in human genome editing discourse

Overtures toward governance of HGE began in mainstream scientific and bioethics discourse in the mid-2010 s, spurred by development of CRISPR-cas9-based genome editing techniques. Development and distribution of these new methods have made precise genome editing much cheaper, easier, and more widely accessible than ever before. Following early development of these techniques, and especially following publication of research involving modification of nonviable and viable human embryos (e.g. Liang et al., 2015, Kang et al., 2016, Ma et al., 2017), scientists and policymakers began to engage with questions about the purposes, cultural meanings, biological, economic, and social risks, benefits, outcomes, and governance of HGE, which had lain mostly unaddressed in governance and policy for decades (Hurlbut, 2015; e.g. National Academy of Sciences and National Academy of Medicine, 2017; Nuffield Council on Bioethics, 2016; Nuffield Council on Bioethics, 2018) .[1]

Since, at latest, the 1975 Asilomar Conference on Recombinant DNA, biotechnology governance norms and institutions have largely disregarded concerns about the potential meanings, purposes, risks, contexts, and ultimate desirability or permissibility of HGE on grounds that 1) such outcomes and meanings could not be predicted and 2) HGE was technically infeasible anyway (Hurlbut, 2015, 2018). Yet, once HGE was finally acknowledged as relevant because it had finally become feasible and cost effective (thanks to no small effort by funders and researchers), governance options were seriously constrained by the advanced state of the technology (Martin and Turkmendag, 2021).

By 2016, genome editing was relatively easy, cheap, and widespread. Both before and after the He announcement, many commentators argued that, given the facility and accessibility of genome editing tools, various types of HGE were nearly or entirely inevitable. He Jiankui himself became a prominent example, as a biophysicist who had taken up newly facile genome editing tools (Greely, 2019; e.g. Church, 2015, Doudna, 2015, Juengst, 2017). HGE, something previously framed as so unimaginable as to be unworthy of serious discussion or preparation, was now discussed as unavoidable. Societies, institutions, and governance frameworks were not prepared to consider its broad social implications, much less to (if desired) prevent it. Nor were they robustly prepared to assess or govern HGE with respect to any but its direct biological effects on individuals (National Academy of Sciences and National Academy of Medicine, 2017).

In our view, this failure of foresight stems from the persistence of three conceptual frames widespread among technology and

[1] Much mainstream discussion of HGE organizes around distinctions between somatic and germline editing, therapeutic or enhancement-oriented aims, and research or implementation. While these distinctions (especially the somatic/germline divide) capture important differences in biology and potential outcomes, all forms of HGE share (with one another, and, indeed, with other varieties of genome editing and biological engineering) important commonalities in institutional and systemic context and orientation. These commonalities correspond to some of the factors most important for the scoping, direction, governance, and large-scale outcomes of HGE, so we do not treat different HGE types separately here. Our aim is not to prescribe particular solutions (e.g. regulatory structures), which would require accounting of and response to the characteristics specific to each variety of HGE. Rather, it is to articulate important questions of governance, political economy, and social context that merit public and scholarly attention.

governance actors. By "frames," we refer to hardened assumptions that undergird perspectives on sociotechnical change by fixing boundaries of attention. First, understandings of scientific knowledge production and technological innovation as essentially unpredictable, inevitable, and universally beneficial—empirically implausible but politically useful for technical communities, their funders, and their beneficiaries—have stifled debate about responsible innovation. Though often stemming from academic research, novel biotechnologies are almost universally implemented through private industry (Lehoux et al., 2014, 2016; Shapin, 2008). Shared interests between industry in seeking profitable new technologies and policymakers in promoting national technological and economic ascendancy disincentivize efforts to shape or constrain innovation in accordance with broader societal interests or values. Attempts to do so, e.g. efforts by European governments to shield their agricultural economies from potential environmental and market-structure effects of genetically modified crops, are often derided as antiscientific and regressive (e.g. Drobník, 2008, Schulman et al., 2020). Under the linear model, such efforts are imagined as futile at best.

These understandings have long served to elide the plasticity and partiality of innovation activities and the thoroughgoing historical contingencies, value-laden decisions, and political contestations that determine their forms (e.g. Bush, 1945; Merton, 1938, 1973; Polanyi, 1962). Deterministic narratives have ignored how programs of knowledge creation and technological development embody the choices and preferences of scientists, technologists, and their material supporters (Bijker et al., 1987; Heilbroner, 1967; Stokes, 1997; Pielke, 2007; Winner, 1977, 1980); and that such choices and preferences could be otherwise. By assimilating these choices and preferences to the inevitable and universally beneficial, narratives of technological determinism and inevitable scientific progress have served as a powerful hedge against scientific responsibility either to society or for long-term outcomes. Adverse effects of innovation are often discussed as "unintended" or "unanticipated" consequences. This depersonalizing phrasing sidesteps the likelihood that many such consequences could be avoided with different intent, or anticipated with different (often, more inclusive and broadly scoped) foresight practices.

Second, and closely linked to the dominance of technical experts in directing research and imagining the futures it may create, an overemphasis on technical predictability has limited the scope of conversation. Potential outcomes of technological innovation are only taken as legitimate topics of discussion if they can be rigorously and quantitatively predicted. Such narrow assessment of research outcomes constrains the horizon of legitimate concern regarding biomedical research and development to the very near-term, the strictly biological, and, often, the individual. Many of the most important potential effects of research—e.g. creation of capacity for novel ways of intervening on human bodies, development of new markets, production of new biological advantages linked to socioeconomic status, or contribution to marginalization of disabled communities—may lie years ahead and involve social, cultural, and economic systems even more complex than human bodies. Such outcomes cannot be accurately predicted, but this does not mean that they cannot be discussed or acted upon.

Third, a reactive stance in governance both derives from and reinforces the prior two themes. Commentators presume that the proper role of policy, for example, is to respond to and ameliorate known problems. Because only near-term biological consequences can be rigorously predicted, this means that broader societal issues are not recognized or addressed until already manifest. This is the classic Collingridge (1980) dilemma: the consequences of innovation cannot be fully known until they manifest and harden, thus only partial and incomplete knowledge is available when governance is most feasible. Contrary to reactive conceptions of governance, however, total knowledge is not a prerequisite for policymaking. Potential societal impacts and controversies can be anticipated based on past and present happenings, and uncertainties can be mapped to support strategic decision-making. Action can be taken to consider potential outcomes of innovation and to intervene on the present systems that produce future outcomes, thus in real time to shape technological change in alignment with societal values. Though outcomes cannot be modeled or predicted in the fashion of merely technical problems (e.g. off-target effects or mosaicism, in genome editing[2]), this does not mean that they cannot be anticipated, especially with knowledge of the actors and aspirations involved in guiding research and innovation. Nor does it mean that they could not be shaped, avoided, or prepared for through concerted action by such actors or by alteration of such aspirations.

But such shaping, preparation, and guidance require investment in modes of anticipation and broad-based capacity-building beyond biological risk assessment led by technical experts. They also require recognition of the plurality of potential futures—something denied by the framework of technological determinism—and of researchers', private actors', policymakers', and publics' agency in imagining and pursuing them. This, too, requires broadly scoped and broadly inclusive ways for researchers, policymakers, and publics to conceptualize and relate to possible futures.

2.2. *Foresight and responsible innovation*

There are, of course, exceptions to the dominant framings we have discussed. Some commentators have overtly critiqued technology-first HGE discussion and governance, advocating for more society-led action (e.g. Bovenkerk, 2015, Hurlbut et al., 2018, Kuzma, 2016). Consensus reports from major science advisory and bioethics institutions (e.g. National Academy of Sciences and National Academy of Medicine, 2017, National Academy of Medicine, National Academy of Sciences, and Royal Society, 2020, Nuffield Council on Bioethics, 2016, 2018, World Health Organization, 2021) have acknowledged the need for forward-looking and publicly responsible efforts to ensure that HGE, if it occurs, produces good public outcomes.

In recent decades, scholarship and practice in "responsible innovation" (RI; Stilgoe et al., 2013) or "responsible research and

[2] Two barriers to practical genome editing are the incidence of off-target edits, wherein the editing intervention causes additional and undesired genetic changes besides those intended; and mosaicism, wherein the editing intervention affects some but not all targeted cells (or affects different cells differently), leading to heterogeneity in genotypes within targeted tissues (Liang et al., 2015; Mehravar et al., 2018; Zhang et al., 2015).

innovation" (RRI), most significantly instantiated in Europe under the Horizon 2020 funding program (Rip, 2018), have drawn together and elaborated more broadly framed and more comprehensive methods for anticipating and shaping technologies' outcomes to public purposes. They have shown that overt strategic engagement with and intersectoral deliberation around a plurality of potential futures can build capacity among researchers, publics, and policymakers to reflect upon the stakes and potential outcomes of research activity. In so doing, such work may help to align research with explicit social values and priorities. But, with few exceptions (e.g. van Mil et al., 2017), these methods and tools have not been taken up and used in address of HGE. Rather, mainstream consensus reports' address of public concerns and the future remains highly focused on the in-principle acceptability of HGE applications in isolation, with little discussion of how such applications might come about or their systemic context.

Future scenarios used in mainstream HGE discussion are essentially moral-philosophical thought experiments; they typically consist of a single, anonymous, featureless patient, a single intervention to be applied to that patient, and nothing else—no discussion of where the patient or the intervention came from, which sorts of patients will be intervened upon, what the intervention costs (financially or socially), for whom, what byproducts or indirect effects its development had on the state of technologies, etc. The German Ethics Council's (2019) rigorous ethical analysis of three potential HGE applications provides a strong example of this style of reasoning, and it is widespread in HGE discourse (e.g. National Academy of Sciences and National Academy of Medicine, 2017, National Academy of Medicine, National Academy of Sciences, and Royal Society, 2020; Nuffield Council on Bioethics, 2016, 2018). Similarly, Nelson and colleagues (2021) review 15 public opinion studies on HGE from 2015 through 2019 and find only one asking participants about their social priorities and concerns about genome editing rather than merely their in-principle acceptance of particular applications to individuals in isolation.

Bioethicists use such simplistic scenarios to ask, "Is this intervention, in the abstract, morally permissible?" Public opinion researchers use similar scenarios to ask, "Will citizens view this intervention, in the abstract, as permissible?" But these are not the only questions worth asking—in part because the moral significance of and public response to biomedical interventions depend to a large extent upon how, where, when, why, and to whom such interventions occur (and do not occur). Address of the broader systemic drivers and consequences of HGE development will require different ways to think about and use possible futures. Responsible innovation methods are well suited for this task. Our project applies one approach to RI, known as anticipatory governance (Barben et al., 2008), to HGE. Anticipatory governance attempts to build capacity in researchers, policymakers, and publics to pursue broadly beneficial outcomes via efforts to anticipate, identify, and respond to emergent conflicts, tensions, or adverse consequences in scientific research and technical development (Barben et al., 2008; Guston, 2014; Selin et al., 2017). Methods for such reflection include expert scenario development workshops (e.g. Withycombe Keeler et al., 2019, Selin, 2008), public forums (e.g. Kaplan et al., 2021; Tomblin et al., 2017), and multimodal public engagements (e.g. Selin, 2015, Selin et al., 2017), among others. We report findings from a component of this project intended to identify "other questions" than the in-principle permissibility on interventions with which governance discourse, foresight exercises, and public engagement alike should engage.

3. Methods: Anticipating human genome editing

We report on one component of a larger, ongoing project incorporating several scenario-based methods. Specifically, the interviews reported on here informed the design and content of an expert scenario development workshop on the possible futures of HGE; and, in combination with the outputs of that workshop and of multiple public "concern gathering" focus groups, have informed the design of several large-scale public deliberations on HGE governance. The interviews derive questions from scenario planning methodologies, asking participants about major initiatives, relevant system properties, and plausible futures. Such topics offer a framework for thinking through a variety of plausible futures to which actors may contribute and with which they may have to contend (Bishop et al., 2007; Ogilvy & Schwartz, 2004).

Thus, in an effort to elucidate the plurality of potential futures for HGE and the factors upon which they rest contingent, our team conducted semi-structured interviews during 2019 and 2020 with 30 scholars and practitioners working on or about HGE. These interviewees were purposively selected based on review of news, grey, and scholarly literature to identify influential voices from different sectors and communities in HGE governance discussion. Interviews were intended to build a multidimensional understanding of the present state and possible futures of HGE by drawing on diverse types of expertise and domains of focus, a practice core to scenario planning techniques (Dannemand Andersen et al. 2021). Interviewees included one journalist; two biotech industry professionals; one historian of the biosciences; four STS scholars; two citizen scientists or "biohackers"; one legal scholar; two philosophers; three futures studies scholars; three bioethicists; seven bench scientists; two clinical scientists; and three policymakers. Twenty-eight were based in the United States, one in the France, and one in the United Kingdom.

Interviews lasted for 60 minutes, were attended by two members of the research team, and were audio recorded, professionally transcribed, and reviewed for accuracy. Interview guides focused discussion on important uncertainties, possibilities, actors, and features of the global landscape in the ongoing development of HGE (Appendix). Team members reviewed interview transcripts to inductively develop a coding scheme identifying important commonalities of topic across interviews (Strauss & Corbin, 1990). Comprehensive results from this analysis are presented in (Barlevy et al., in press). Codes were validated by double independent review.

The present paper more deeply reports on one subset of inductive themes, i.e. important dimensions of potential longer-term variation in plausible futures (Ramírez & Selin, 2014). This subset includes comments wherein interviewees expressed uncertainty, ignorance or disagreement about likely outcomes, largely in responses to an interview question about important uncertainties in the future of human genome editing (Question 5, Appendix). In articulating these uncertainties, we supplement interview data with information drawn from prior literature review (Nelson et al., 2021).

In the following section, we present seven major uncertainties articulated by interviewees, presented as "open questions." These are uncertainties about the possible development of HGE, and efforts to answer them support reflexive exploration of HGE's eventual shape and outcomes. These are not questions to be answered definitively, pursuant to prediction of a single future state. Nor are they intended as a definitive set of "the essential questions" to be answered about HGE futures. Rather, they are designed to probe dimensions of uncertainty, exploration of which may help actors within the HGE space to understand the plurality and complexity of potential futures; and to derive actions which may protect and promote their values across a variety of such futures. The following section summarizes the content and import of each question.

4. The Seven Questions

4.1. How might genome editing's accessibility and ease of use affect development and governance?

On a phone-filmed internet livestream in October 2017, bare-handed, dressed in a t-shirt depicting a cartoon plague doctor and sipping Scotch from a flask, self-identified biohacker and entrepreneur Josiah Zayner injected himself with a CRISPR-cas9 compound in an effort to, as he told his audience, "give [himself] bigger muscles" (Zayner, 2017). He expressed a desire to make genome editing technology "available, now," doing "whatever it takes." Zayner's company, The ODIN (The ODIN, 2020), sells DIY genome editing gear online, including a product labeled "Bioengineering 101 Beginner Kit and Video Lectures – No Experience Needed" (priced 299 USD at time of writing) and "Genetic Engineering Home Lab Kit" (700 USD, on sale). Shortly after his livestream stunt, Zayner told Buzzfeed reporter Stephanie Lee (2017), "I want to live in a world where people get drunk and instead of giving themselves tattoos, they're like, 'I'm drunk, I'm going to CRISPR myself'"—though, a few months later, he expressed regret at the example he had set and concern that overenthusiastic biohackers might eventually harm themselves or others.

Zayner is only one of many "nontraditional actors" who, thanks to CRISPR-cas9-based techniques' low cost and broad accessibility, are now able to experiment with genome editing outside major centers of biomedical innovation and conventional forms of research governance. Some of the experts in our interview group labeled He Jiankui, originally a biophysicist, as another: a researcher who, by virtue of the relative ease of CRISPR-cas9-mediated genome editing, was able to quickly pick up and use the tools without attracting major attention or scrutiny. Our interviewed experts nearly universally felt that CRISPR-cas9-based genome editing is qualitatively different from many previous technoscientific developments in that it is not bound to high-cost, high-intensity, highly skilled research centers. Instead, a dedicated layperson, like Zayner, can do it in their garage.

Globalized trade and communication infrastructures significantly reduce geographic localization of technical knowledge and material tools, and our experts expressed pessimism regarding the ability of existing institutions' and governance mechanisms' ability to surveil or regulate experimentation. "[P]eople [can] just. take risks which no ethics committee would allow a researcher to take," said one prominent legal scholar. "That. creates a new channel, and [with] social media maybe it gets spread very differently and much more quickly than those sorts of things previously had. Quite how you get a handle on that I'm not sure, I'm afraid." Others worried that unregulated, nontraditional actors might, through some disastrous experiment, draw public or policymaker backlash to genome editing. In scholarly literature, low technical barriers to genome editing combine with problems of international governance in arguments that governance cannot stop genome editing, and that efforts to do so would only drive it underground and to poorly regulated—thus, implicitly, less responsible—jurisdictions (Church, 2015; Doudna, 2015; Ormond et al., 2017).

It is highly important and more uncertain than ever before who will conduct potential research, development, and implementation in HGE; and how regulatory oversight can or will respond to the weakness of technical barriers to its conduct; and how nontraditional actors themselves may develop formal or informal ethical and regulatory norms. The backlash scenario that researchers fear is only one of many ways in which nontraditional actors could affect HGE development. HGE actors would do well to explore and prepare for others.

4.2. How high a priority is human genome editing for research? For healthcare at large? As an issue of socio-technical governance?

Though HGE is dramatic and evocative, it is far from the only potentially important use of genome editing techniques (Charo & Greely, 2015). CRISPR-Cas9-based techniques are being used in agricultural experimentation, and the possibility of "gene drive" alterations used to modify entire populations (e.g. of insect pests) has attracted significant attention in scholarly communities (Delborne et al., 2018). Nonhuman genome editing could have significant implications for biodiversity, ecosystem resilience, and human health. With respect to funding, public attention, research hours, and governance focus, HGE also competes with other potential public or individual health interventions, ranging from personalized medicine, other research tools and pathways to questions around food poverty and environmental pollution (cf. Bozeman & Sarewitz, 2011, Sarewitz & Pielke Jr, 2007). One interviewed bioethicist was quite explicit about this tradeoff, arguing that genome editing should not be an investment priority for society at large but should be a discussion and governance priority for researchers and policymakers:

"In the big scheme of things, [human genome editing is] not the most urgent priority for human health. There are certainly a lot more pressing questions like climate change, clean water, basic social determinants of health. Gene editing is way down the list from those, but on the cutting edge of biomedical research, particularly in genomics and genetics. It's a game-changing technique. So there's the big picture–no, we should put our money elsewhere–but in the more focused picture, yes, this has got to command the attention of people in that field because it makes things so much easier."

Even within biomedical research investment and governance, attention to HGE stacks up against other important topics, e.g. responses to public health crises and inequalities in access to health care. Investment in conduct or governance of HGE will necessarily

involve opportunity costs. Tight focus on HGE in public and policy discourse may neglect equally or even more impactful developments within and without both genome editing and biomedicine—including research efforts which, due to the platform nature of many genome editing technologies, might, "under the radar" build capacity for fraught and controversial HGE activities though research and development with other aims (e.g. agriculture).

Though it may seem counterintuitive, discussions about HGE should keenly attend to the world outside HGE, with serious attention paid to the opportunity costs of financial, political, and imaginative investment in the conduct or the governance of HGE. Publics, policymakers, and scholars should explore the sorts of developments which might evade scrutiny if scholarly, policy, and public focus remain too tightly on HGE, and should explore the ways in which concerns, possibilities, and actions relevant to HGE are also relevant to other health issues and other genome editing uses.

4.3. What interests have shaped, could shape, or should shape research and development of genome editing technologies? How, and to what ends?

We are far from the first to observe that biomedical research is big business, and that the cultural archetype of the monastic, disinterested researcher has over the last 60 years given way to the mythos of the enterprising scientist-entrepreneur (Shapin, 2008). Researchers and biotech startups woo funding agencies and private investors with extravagant claims about their technologies' revolutionary potential (Brown, 2003; Hilgartner, 2015). Major federal funding initiatives are justified with reference to a universally beneficial "bioeconomy" (White House, 2012). Meanwhile, health research disproportionately focuses on the ailments of wealthy populations (Ramsay, 2001), and the products of biomedical innovation often lie far outside the means of most patients (Douglass et al., 2018). Alongside discussion of human applications, genetic engineering for agriculture continues to boom, contributing to development of "platform" genome editing technologies which could be reapplied in humans.

The development of the HGE space, the outcomes it produces, and the values it supports, crowds out, or undercuts will depend upon the interests—economic, scientific, geographic, political—that come to control it and the tools by which they do so. Some interviewees suggested that changes in the dynamics of biotechnology innovation systems have rendered old governance mechanisms increasingly invalid. As one clinical researcher put it:

"[Y]ou may not be aware of is how much research is being done, whether it's [memory or] anti-aging or go down a huge list that you don't know about and we will never know about because this stuff is not being published. It's now more on the private side, and there's no need for publication. We're hearing about these things, some drabs, you know what I mean? So out of the blue, you're going to hear about some treatment somewhere or something you've never heard about through the medical literature."

Older systems of scientific governance, e.g. mutual oversight through open literature, may be increasingly irrelevant in a world of proprietary research and development. This is only one of the ways in which the development of powerful economic interests in biotechnology has changed the research landscape. One scholar of science and technology studies (STS) expounded:

"I think there are serious economic questions about who is doing the work with what incentives. [Human genome editing has] been a largely academic field so far with minimal private sector involvement. [N]ow that you have some therapies brewing[, private sector involvement] is increasing. you have patents and licenses. The economic incentives could drive the therapies in particular directions, especially in the absence of any kind of regulation or clear guidelines in terms of what kinds of stuff should be funded or what shouldn't be funded."

Financial interests (of nations, corporations, or individuals) are not the only ones potentially at stake in HGE. Demands for optimization of military personnel's performance create potential incentives for military investment in HGE-based human enhancement (Greene & Master, 2018). Sunk costs and the exigencies of career advancement incentivize researchers to push HGE efforts forward, while patient groups and disease lobbies may (accurately or inaccurately) see in HGE hope for treatments or cures. Several of our interviewees expressed concerns that a hunger for scientific novelty and prestige could induce HGE researchers to go too fast or too far—with, again, He Jiankui interpreted as central example. Meanwhile, some scholars and activists express concern that development of HGE could reinforce genetic essentialism, eugenics, or marginalization of genetically disabled persons, expand health disparities, or place pressure upon persons to modify themselves or their children (German Ethics Council, 2019). Others have observed that HGE raises basic questions of orientation toward human lives and futures, including what actors and forms of reason possess authority to define lives worth living and futures worth pursuing (Jasanoff & Hurlbut, 2018).

Different types of actors have access to different sorts of tools—financial investment, regulation, data collection and display, public demonstration—with widely varying applications. Different combinations of interest and tools will produce different outcomes. Both militaries and venture capitalists can guide innovation through investment, but these two groups would likely desire different sorts of HGE applications and distributions thereof. Meanwhile, international standard-setting bodies and activist groups might both wish to prevent human enhancement, but one might do so through research registry and professional pressure, the other through public demonstration and political action. These examples are simply meant to illustrate that meaningful engagement with a plurality of potential futures requires serious contemplation of who wants what in and around HGE, the tools which they could use to pursue their interests, and the different ways in which struggles between them could play out.

4.4. How might norms around health and disability evolve over time?

The possibility of HGE intersects with norms around health and disability in several ways. Scholarly discussion of HGE tends to take therapeutic and enhancement applications of HGE as fundamental categories of analysis (Brokowski, 2018). Ethicists and policy scholars offer different recommendations for therapeutic and enhancement applications (e.g. German Ethics Council, 2019; National

Academy of Sciences and National Academy of Medicine, 2017; Nuffield Council on Bioethics, 2016). Public opinion studies ask respondents to separately rate their responses to HGE used for medical therapy and for human enhancement (e.g. Pew Research Center, 2015; Scheufele et al., 2017; Whitman et al., 2018). But the boundary between therapeutic and enhancement applications is nebulous, contextual, and dynamic. Pathologization of biological phenomena currently regarded as normal—e.g. aging (Scott & DeFrancesco, 2015; Kostick et al., 2019)—could significantly shift the enhancement-therapy boundary.

Furthermore, several of our expert interviewees observed that the tools and knowledge used for therapeutic interventions could be relatively easily turned to enhancement attempts as well. Even if we presume a meaningful distinction between therapy and enhancement, development of therapeutic capacity—or of techniques for editing nonhuman genomes—may well necessarily be development of capacity for human enhancement (Juengst et al., 2018).

Our interviewees also echoed some scholarly discourse in voicing concerns that the availability of treatments (preventative or otherwise) for certain genetically-based conditions might reduce societal acceptance of those conditions, contributing to marginalization of these groups and placing pressure on persons to modify themselves or their children (German Ethics Council, 2019; Nuffield Council on Bioethics, 2018). A biohacker observed that "saying, 'We want to genome-edit out errors,' is calling [disabled persons] errors in society." A clinical researcher asserted that "we should never get to a point where somebody would feel like they have to [use human genome editing]." He continued, "[i]f we get to a path where parents feel like that's a 'should,' I think somewhere we've made a mistake."

4.5. How might scientific authority in society evolve over time?

For decades, scholars and scientists have described growing alienation between scientists and publics, read through phenomena including anti-nuclear protests, patient group advocacy, genetically modified food activism, climate change debate, stem cell research controversy, anti-vaccination movements, and biohacking (Epstein, 1998; Felt & Wynne, 2007, 1992, 2001). These tensions erupted into mass media prominence in 2016, when traded accusations of "fake news" and assertion of "alternative facts" within the U.S. political scene led some commentators to declare the advent of a "post-truth" era (Sismondo, 2017). Though we feel that such melodrama overstates the novelty and degree of this phenomenon (see Jasanoff & Simmet, 2017), the always-partial monopoly of traditional scientific expertise over truth claims, technical development, and the framing of public discourse does seem in important ways to be decaying (cf. Ezrahi, 1990, 2004, 2012).

It's unclear if this trend (if trend it is) will continue, and, if so, what it might mean for the development of HGE. Many expert commentators fear blunt political or public backlash to prospective genome editing uses, while others express concerns over laypersons attempting to take biotechnology and medicine into their own hands (e.g. Adashi & Cohen, 2015, Ormond et al., 2017). Many take it as important that expert understandings of genome editing propagate among the public, and that experts rather literally set the (linguistic) terms of debate (e.g. Merriman, 2015, Nelson et al., 2015, O'Keefe et al., 2015). One interviewed bioethicist linked both public skepticism toward science and lay experimentation with a decline in trust in scientists:

"I see a common theme between [biohacking and lay skepticism toward science]. I'm sure there are demographic and sociological differences between the people involved. But the common theme is reduction of trust. or maybe it's just a reduction of social status for scientists and science on both ends of the spectrum. People are saying, 'Why should we believe these guys and let them do whatever they want just because they're experts? Our views are just as important as theirs, so either we don't have to listen to them,' or 'They should listen to us and let us get involved in the design and conduct of science.'"

One biohacker felt that rapid development of HGE, possibly against objections from large public communities, could increase such distrust:

"[O]ver the last ten years. We've lost a lot of public faith and trust in science. Granted, a lot of people believe in climate change, but a lot still don't. I think rolling out new technologies that are so potentially radical, even if you understand the science behind them, doesn't give back public trust. I think it increases distrust."

The possibility of HGE has already elicited different responses from different publics and will likely continue to do so in the future. What is less clear is how such responses will interact with an apparent decline in trust in experts; where and how publics will develop their own understandings and views of genome editing; and how experts themselves might respond to a sense that their relationships with policymakers and publics are changing.

4.6. Are undesirable uses the cost of desirable ones?

As discussed above, CRISPR-cas9-based genome editing is a "platform technology," with many applications across different organisms, purposes, and academic and industrial communities (Martin et al., 2020). Further developments and many prospective interventions could be similar: broadly applicable tools, easily put to uses unexpected by their developers. Development of tools for experimentation in animals could build capacity for intervention in humans. Treatments designed for therapy, e.g. muscle growth promotion for treatment of muscular dystrophy, might provide possibilities for enhancement (Juengst et al., 2018). As one interviewed bioethicist put it:

"[A] lot of [enhancement-capable] ideas are being pursued [under the idea of therapy]. The resistance to pain for the prevention of chronic pain and disabling diseases or the ability to function with no health effects on less sleep to prevent sleep deprivation and health problems. Or the prevention of cognitive decline by slowing down the aging process. [T]hose all sound kind of like the classic examples of the enhancement interventions we said we never wanted to touch. [And w]e're going to have to face the fact that some. preventive interventions are likely to raise the same ethical questions that we used to talk about under the category of enhancement."

Several interviewees found it implausible, particularly under structures of military, corporate, or even athletic competition, that genome editing capacities developed for sanctioned ends would not also be used for more controversial ones (to say nothing of how boundaries between acceptable and unacceptable uses would be drawn or enforced in the first place; see Section 4.7). One researcher with experience in competitive athletics felt this was a foregone conclusion, telling us, "Athletes are doing things to their bodies that you would never believe. They are injecting themselves with viruses that carry genes. I mean, this is going to be beyond. any kind of academic or institutionalized kinds of things. across the world." Therapies offering enhancement potential to individuals unafflicted with their target diseases could likely be applied "off-label" by seekers of competitive edges, whether high-performance athletes or military institutions. Conversely, enhancement tools developed under the mandate of military necessity could filter out into the civilian economy or black market.

Other interviewees expressed concerns that capabilities developed in little-scrutinized areas of practice could be swiftly transferred to more fraught ones; or that market demand and jargon-centered hype could lead to a proliferation of unregulated (and potentially ineffectual or harmful) treatment, as in the case of grey-market "stem cell" clinics across the United States (Frow et al., 2019; Turner & Knoepfler, 2016). A science and technology studies (STS) scholar observed, "the history of preimplantation genetic diagnosis and stem cells. shows us that. there are a lot of lone rangers, right? And there are incentives to being those lone rangers, and those lone rangers pose significant risks to the public, right?".

Social-media-based harassment and disinformation campaigns amply illustrate the ways in which "platform" technologies can enable harmful or undesirable efforts as well as beneficial or sanctioned ones. It is unclear whether or how genome editing development could avoid such multiple uses, or whether platform developers could or should be held responsible for them.

4.7. How will authority and responsibility be distributed among actors?

Most expert statements regarding HGE make at least some overtures toward public involvement in governance, recognizing that control over past so-called "emerging technologies" has belonged largely to technical experts in what some term a violation of democratic norms (Jasanoff, 2018; e.g. Baltimore, 2016, National Academy of Sciences and National Academy of Medicine, 2017, Ormond et al., 2017). However, they rarely discuss in detail the specific roles that publics should play in genome editing governance or the mechanisms by which they might do so. More broadly, it remains highly uncertain how authority over many different topics (e.g. patient rights, aspirational futures, desirable processes, sanctioned ends, and distinctions between therapeutic and enhancement interventions) will be distributed among different actors and constituencies within and without HGE practice, and how disagreements between different actors may be resolved. It is similarly unclear who will be held responsible (and how, and by whom) for securing public or private goods and preventing or ameliorating harms in and around HGE, and who will bear the costs and risks of development, implementation, or oversight and prevention.

One of the central questions raised about governance throughout our expert interviews simply regarded who will be "at the table." Several interviewees expressed concern about underrepresented voices in the genome editing space, some of whom may not even immediately see the relevance of HGE to their concerns:

"[I]ndustrialists are important, but I don't know that you can trust what they say. [P]rivate industry will sell some story about self-regulation and how it's great. I think it's interesting to think about organizations that don't, or stakeholders or perspectives in society that are very important, but that tend not to participate in conversations about CRISPR. That might be environmental activists., [i]t might be civil rights folks or people who are interested in racial justice. Who are important figures in society that represent citizen concerns? Who [raises or represents] concerns about economic inequality?"

Another interviewee put the focus slightly differently: "I think the big uncertainty around governance is going to be, to what extent are the true believers in the inevitable good of technological innovation going to be allowed to rule the roost?. [Those folks] inhabit a pretty privileged role of being able to believe that only good comes from their intentions. I think that [regular people] are going to have zero say."

Experts and scientific institutions across the world have at least paid lip service to avoidance of such a future. Nonetheless, some critiques suggest that overtures toward "public engagement with science," like other forms of "citizen participation," can in practice can work simply to re-legitimate preexisting authority without genuine citizen empowerment (Arnstein, 1969; Wynne, 2006). The question of "who" is inseparable from that of "how"; different forms of governance, e.g. by institutional review board, expert panels and reports, scholarly standard-setting, public polling, deliberative forum, and market competition, emphasize different values and empower or disempower different voices. Those concerned with HGE should carefully reflect upon the commitments and trade-offs baked into particular mechanisms of governance, and the ways in which they continually allocate costs, benefits, rights, responsibilities, and the authority to define and pursue desirable futures.

5. Uncertainty, complexity, and agency

These thematic questions draw out broad contextual, systemic, and political issues elided by focus on inevitabilities, technological trajectories or risk-based regulation. By articulating them, we identify some important areas of attention for public and policy debate. Some of these questions have received attention in scholarly literature. Others have not. Either way, we feel that these are the sorts of questions that could and should have been asked much earlier in the development of HGE, and which still require much more consideration.

Interestingly, our themes cut across the technical categories by which many ethicists and scientists have sought to partition normative issues in HGE development, e.g. distinctions between germline and somatic, and between therapeutic and enhancement-

oriented, editing (see, e.g., National Academy of Sciences and National Academy of Medicine, 2017; National Academy of Medicine, National Academy of Sciences, and Royal Society, 2020). The broad relevance of our questions illustrates that many of the institutional and systemic factors that shape technologies' outcomes, e.g. the proliferation of "platform technologies" or incentives of national, commercial, and military competition, apply across fairly different technological categories. Moreover, developments in one application of genome editing are likely to affect developments in others. Thus different applications of genome editing (and other technologies), even if technically and morally distinct, cannot for practical purposes be thought about and governed wholly independently from one another. If, for example, we want therapeutic editing, we must, as Juengst and colleagues (Juengst et al., 2018) observe, decide whether it is worth the likelihood that many therapeutic techniques could be turned to enhancement as well.

Our questions offer a corrective to several values and discursive habits that impede productive anticipatory governance. Popular and scholarly discussion of the "He debacle," and of HGE in general, has rehearsed longstanding cultural narratives wherein scientific and technological activities race ahead to create the future while society, law, norms, and forms of life stumble and scramble to keep up. CRISPR-cas9 co-discoverer Jennifer Doudna (2015) describes HGE less as a novel human activity than as outgrowth of the 40-year evolutionary history of recombinant DNA, while Nobel laureate David Baltimore (2016, p. 35) considers it to be "part of a historical process that dates from Darwin and Mendel's work in the nineteenth century." Now that "the unthinkable has become conceivable," says Baltimore, society must face and respond to "the questions that arise." Neither Baltimore nor Doudna addresses the fact that it was diligent, human work that made HGE conceivable, that raised its attendant questions, and that will produce any outcomes, good, ill, or both, which come of it. Their framing does not acknowledge that such work could have played out differently or not at all. Nor does it recognize how discussions held and governance mechanisms developed might have prepared for or shaped its eventual fruition.

As an alternative to determinism or fatalism, the questions drawn from our expert interviews illuminate important dimensions of uncertainty through which we may imagine different futures for (or excluding) HGE. As examples, they reveal many precarious possibilities and expose a variety of tensions and trade-offs between different hopes, concerns, and interests. They cast light upon the present and potential configurations of the human systems and relationships which will determine HGE's eventual shape and outcomes. They illustrate that, while it is not possible to predict and plan for a single, certain future, it is possible to draw on present knowledge to articulate a variety of plausible ones. Such anticipatory knowledge can provide grounds for informed, proactive governance to preempt harmful innovation outcomes and promote beneficial ones; and produce space for robust dialogue about which are which.

In our view, this reclamation of social agency is essential to effective innovation governance. Understandings of innovation as autonomous and unpredictable remove a sense of agency and accountability among research actors. Such impoverished forms of imagination deny even experts, let alone laypersons, the power to govern our science and technology. In practice, they encourage research actors to abdicate responsibility for their actions' consequences and deny others the opportunity to influence them or hold them accountable. Recognition of the true complexities of scientific research and development—their status as contingent, human enterprises fostered and driven by webbed landscapes of institutions, communities, and interests—replaces the invisible hand of Progress with the real hands and minds of humans, encouraging us to reflect on how we use them. An anticipatory governance approach gives up demands for perfect knowledge and total control, and their concomitant myopia and reactivity, in favor of preparation, reflexivity and adaptability. It seeks strategies and responses robust to variance across the types of questions treated above.

We must address certain limitations of our work. As others have argued, a move beyond expert opinion may open up richer and more nuanced understandings of responsible innovation and possible futures (Stilgoe et al., 2013; Stirling, 2007). We note that our data derive from (mostly U.S.-based) expert perceptions and thus replicate one aspect of the failures of foresight we critiqued at the outset. While we sought to include experts from a wide range of disciplines and with diverse professional experiences, our interview sample did not include many other voices that would create a more robust accounting of key issues. Patient advocates, persons caught without access to basic healthcare, business leaders, and families of potential gene editing patients would all enrich the conversation. The public deliberations into which these interview results will feed will aim to expand the range of voices empowered to frame concerns and priorities about HGE. Nonetheless, these questions already reframe the system dynamics and potential permutations of HGE in more expansive fashion than do conventional, risk-centered discourses.

Readers knowledgeable in scholarship of science and society will recognize that several of our questions seem to be cases of more general questions which often arise around emerging technologies. This result may be an artifact of the analysis process of team members steeped in STS discourse around emerging technologies. It is possible that, looking into the interview data, we focused on themes resonating with our literature-conditioned sensibilities. A more charitable view might suggest that prior discussions and prior literature have focused on similar questions because these are the sorts of persistent issues which arise around ambitious programs of technoscientific innovation.

Regardless, the aim of this work is practical rather than theoretical—though these are old questions for STS, they are relatively new ones for HGE practitioners, ethicists, and policymakers. This paper aims to illustrate the utility of a reorientation away from traditional discourses of patient-focused risk-benefit analysis to a more robust and multidimensional exploration of plausible futures. Even well-established STS concerns and insights are not widespread in HGE governance discourse, and even the most theoretically creative scholars are not above translating old insights for a new audiences (e.g. Jasanoff, 1992).

On the practical level, expert discourse and public engagement about the development and governance of HGE would benefit from address of our and similar questions. Unlike the abstract questions of in-principle permissibility that have framed much HGE discourse, these questions focus attention on the ways in which the structures and dynamics of innovation ecosystems shape the outcomes of particular technological innovations, and in turn emphasize trade-offs and ripple effects in innovation and governance efforts. International summits, consensus reports, public engagements, opinion studies, research policy deliberations, and perhaps even institutional review boards should ask what interests are driving and likely to be served by HGE development, how HGE might contribute to

or be affected by shifts in norms about disability and aging, and whether the possibility of new therapies is worth the danger of enhancements or proliferation of bioengineering capability. We have ourselves productively employed the questions articulated here in the framing and design of an expert scenario development workshop and public focus groups and large-scale deliberations, all scoped to elucidate important possibilities and public concerns and preferences in HGE (Barlevy et al. in press; Nelson et al. 2022; Tomblin et al. 2021).

We do not know how best to operationalize attention to these sorts of broader, systemic questions in the polycentric, international ecosystem of biomedical innovation and governance. Even the European Union's high-level commitment to responsible research and innovation has had limited effects on the ground-level practice of European scientists and technologists (Novitzky et al., 2020). But for researchers and practitioners interested in addressing the systemic drivers and consequences of HGE, our questions can serve as a resource. This paper also re-illustrates the capability of systemically framed, future-oriented, multidisciplinary interviews to elucidate the societal dynamics of emerging technologies in ways that longer-standing approaches in bioethics and the biosciences do not. The "seven open questions" exemplify the ability of contemporary foresight methods to identify important topics for discussion, concern, preparation, and intervention well in advance of their full manifestation, i.e., before it is already too late.

We hope that these alternative frames for contemplation of HGE futures may help practitioners, policymakers, and publics to expand conceptions of the stakes, impacts, and shapers of HGE innovation and to improve the richness and scope of governance discourse. In-depth interviews with a diverse array of expert stakeholders designed to clarify and question implicit assumptions can disrupt constraining, deterministic conceptions of technological change. By interrogating taken-for-granted tropes about socio-technical change, such inquiries can open up space for new kinds of deliberations and governance interventions. Moving beyond the cover of inevitability enables rich inquiry into mechanisms of agency and debate about alternatives. Instead of relying on the grooves of presumed technological trajectories, deliberation can explore how things could be otherwise. Such reflexive questioning can enable actors to shift from away from a merely risk-based, regulatory understanding of control and agency. These types of reframings permit a deeper, more holistic, and more productive form of technology assessment. Scenario-based methodologies create space for more inclusive, responsible and critical discussions in governance of emerging technologies.

Originality and ethical review confirmation

We confirm that this manuscript has not been published and is not under consideration elsewhere. We also confirm that the research upon which this manuscript is based has been subject to appropriate IRB review. Last, we declare that we have no competing intellectual or financial interests in the research detailed in the manuscript.

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Appendix. : Interview protocol

Domain 1: Personal and professional background and relation to human genome editing research.

1. To start, could you briefly tell me about your role and your personal or professional relationship to human somatic or germline genome editing research?
2. In your view, is human genome editing a priority for biomedical science and human health? Why or why not?

Domain 2: Anticipatory states

3. Before we turn attention to the future, let's explore the past. In your view, what have been the pivotal events and developments in human genome editing? We'd like to hear your thoughts both about recent examples, as well as any prior developments that have been critical, such as gene therapy.
   a. Are there any events over this history that have surprised you?
4. What plausible advances in science and medical care might we see from human genome editing in 10 years? 20 years?
   a. Prompt: What effects might we see from these advances?
5. Next, let's explore some of the main uncertainties. Presumably there are a range of variables and constraints that are likely to impact and shape the use of genome editing, both technological and non-technological.
   a. Let's start with the technological ones—what do you see as likely to be the most influential? (Prompt: how might other emerging technologies intersect and interact with human genome editing?)
   b. What about the non-technological variables that are most likely to impact these technologies? In this research, we are exploring the broader context that surrounds the technology, and so are curious about the role of changing social and political values and

movements, economic structures and incentives, governance, and regulatory regimes. What non-technological variables are likely to be the most influential in shaping the future of human genome editing?

6. What factors do you think aren't on people's radars that should be? What variables have current debates failed to adequately consider?
7. Which stakeholders do you see as most influential in decision-making about these technologies? How, if at all, do you envision this changing in the future?
8. What concerns you most as you consider the future of human genome editing?
   a. What are the key social, ethical, legal, economic or policy questions that MUST be resolved? [Alt framing: In your view, what important issues about human genome editing will we still be grappling with in 2050?]
9. If you were benevolent dictator, what action would you take to improve the field of human genome editing for the future?

Domain 3: Open ended.

10. We've had a lot of questions for you. What haven't we asked you about that we should be considering regarding the governance and future use of these technologies?
11. If we were to speak to two experts or other thought leaders about this issue, who should we talk to, and what should we make sure to ask them?

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