### Title

Reactions to the National Academies/Royal Society Report on *Heritable Human Genome Editing*.




### Journal

The CRISPR journal, 3(5)

### ISSN

2573-1599



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### Publication Date

2020-10-01

### DOI

10.1089/crispr.2020.29106.man

Peer reviewed


HHGE
Highway

The CRISPR Journal
Volume 3, Number 5, 2020

DOI: 10.1089/crispr.2020.29106.man

The CRISPR Journal

PERSPECTIVE

# Reactions to the National Academies/Royal Society Report on *Heritable Human Genome Editing*

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**Abstract**

In September 2020, a detailed report on *Heritable Human Genome Editing* was published. The report offers a translational pathway for the limited approval of germline editing under certain circumstances and assuming various criteria have been met. In this perspective, three dozen experts from the fields of genome editing, medicine, bioethics, law, and related fields offer their candid reactions to the National Academies/Royal Society report, highlighting areas of support, omissions, disagreements, and priorities moving forward.

## Introduction

In September 2020, a major report titled *Heritable Human Genome Editing* (HHGE) was published by the National Academy of Sciences, the National Academy of Medicine, and Britain's Royal Society.[1] It was triggered by the alarming reports in November 2018 of the birth of gene-edited twins in China.

The 18-member HHGE commission was co-chaired by two eminent human geneticists, Dame Kay E. Davies (University of Oxford) and Richard P. Lifton (Rockefeller University), and compiled the report over more than a year of meetings and deliberations. It offers a translational pathway for the limited approval of HHGE under very particular circumstances and assuming various criteria have been met. A separate commission, under the auspices of the World Health Organization (WHO), will soon issue a related report on the ethics and societal considerations surrounding HHGE.

The HHGE report follows the release of more than five dozen ethics statements related to the science and ethics of HHGE issued over the past few years.[2] However, in virtually every case, those reports were dealing with the hypothetical questions posed by preliminary research experiments conducted on nonviable human embryos. That changed in November 2018, with the revelation that twins had been born carrying germline-engineered variants at the *CCR5* locus. (A third gene edited child was reportedly born about 6 months later.) Despite widespread scientific and societal condemnation of these actions, the possibility remained that other researchers or clinicians might attempt to perform a similar procedure.

In this perspective, we invited some 50 experts from the fields of genome editing, medicine, bioethics, law, and related fields to briefly share their candid reactions to the HHGE report, highlighting areas of support, omissions, and priorities moving forward. We received responses from three dozen sources.

The comments are grouped according to a few broad themes that emerged after submission. (Comments have been lightly edited in some cases for length and/or clarity. The views represented are personal and do not necessarily reflect the authors' universities, organizations, or affiliations.)

## Group I: General Support for the Report's Recommendations

### **Jennifer Doudna** (University of California, Berkeley/HHMI)

#### Decision trees for international standards

The HHGE report underscores what most researchers in this field are aware of and agree on: There must not be any use of germline editing for clinical purposes at this time. It clearly lays out various decision trees to help

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(Credit: Mon Oo Yee.)

determine the types of studies, human trials, and settings that might allow germline editing, but I am struck by the inclusion of diseases that can be already managed such as cystic fibrosis.

The report also has a deterrent effect. For any bad actors looking to misapply the technology, it is virtually impossible now to claim that they did not know about the international guidelines or were somehow operating within published criteria. The whistleblower mechanism will help uncover unethical experiments happening in the shadows.

The bottom line is that CRISPR technology is in too early a stage for human germline applications, and we do not understand well enough how it works in human embryos. We must continue an inclusive, transparent public dialogue. This research and associated statements and discussions not only educate and prevent abuse of this promising technology but also provide the details and context to develop international standards that individual countries can align with to ensure appropriate regulation and enforcement of responsible use.

"The HHGE report underscores what most researchers in this field are aware of and agree upon: There must not be any use of germline editing for clinical purposes at this time."

—Jennifer Doudna

*Jennifer A. Doudna, PhD, is a Howard Hughes Medical Institute (HHMI) Investigator at the University of California Berkeley; cofounder of the Innovative Genomics Institute; cofounder of several companies, including Caribou, Editas Medicine, and Intellia Therapeutics. She shares the 2020 Nobel Prize in Chemistry with Emmanuelle Charpentier.*

## **Feng Zhang** (Broad Institute/HHMI)

### Inspiring a future to improve lives

The recent HHGE report contains a number of specific recommendations to guide the decision of if and when to pursue this procedure. Although the overarching

message—that it is premature to implant edited embryos for the use of a pregnancy—remains the same as it did in a related National Academies report from 3 years ago, the current report offers substantially more detailed guidance on how trials of HHGE should proceed. This reflects the continued advances in gene-editing technology, early success of treating patients with somatic gene editing, and increases in our knowledge of human genetics. It may also reflect the fact that in the intervening 3 years, HHGE has been reported.

Thus, despite the bottom line, this report discusses in-depth recommendations for proceeding with germline editing in limited circumstances, perhaps aiming at getting ahead of any other editing attempts. Importantly, the report also emphasizes the fair and equitable access to this technology and acknowledges that unique cultural values must be considered. The report is also an inspiration for a future where the commitment to maximizing human benefit and trust in science transcends international boundaries to improve the lives of those suffering the most.

"The report is also an inspiration for a future where the commitment to maximizing human benefit and trust in science transcends international boundaries to improve the lives of those suffering the most."

—Feng Zhang

*Feng Zhang, PhD, is a core member of the Broad Institute; James and Patricia Poitras Professor of Neuroscience at MIT; an HHMI Investigator; and cofounder of several companies, including Editas Medicine, Beam Therapeutics, and Sherlock Biosciences.*

## **Eric Topol** (Scripps Research)

### A vital and welcome synthesis

Genome editing is unquestionably the most important biotechnology advance of our lifetime. But precise editing of our genome to potentially cure rare diseases and until now incurable conditions represents the ultimate positive impact of this two-edged sword in medicine. However, it can also be applied for HHGE, which carries the potential liability for irrevocable and dangerous transgenerational impact. There is so much more to learn before we embark on this, particularly capitalizing on its precision promise to preempt off-target editing.

"A vital and welcome synthesis of our current knowledge base and shortcomings"

—Eric Topol

The HHGE report is a vital and welcome synthesis of our current knowledge base and shortcomings, providing very useful guidance and recommendations that should help prevent reckless experiments in people and advance the science needed to eventually proceed with HHGE safely and successfully.

*Eric Topol, MD, is executive vice president at Scripps Research, La Jolla, CA; founder and director of the Scripps Research Translational Institute; and the author of* Deep Medicine *and* The Patient Will See You Now.

## **Renzong Qiu** (Chinese Academy of Social Sciences)

### A wonderful report beyond expectation

The report on HHGE (drafted by the International Commission on the Clinical Use of Human Germline Genome Editing) is a wonderful report beyond my expectation. After the 2018 Hong Kong Summit was tainted with the notorious He Jiankui incident, there has been a lot of worry in my mind that the incident may negatively impede the progress of the promising genome-editing technology. The HHGE report makes me confident in preventing the reappearance of a second He Jiankui-like scientist.

Meanwhile, we still take positive and active steps to prepare conditions under which genome editing could be responsibly used in the clinic. I do not agree with some of my scientific colleagues who complain that the report leaves them such a narrow and confined translational pathway to proceed in clinical use. I believe that only with such a narrow translational pathway can we ensure we move into clinical use with scientific validity and ethical acceptance.

The other remarkable point is that at the stage of clinical use that will impact future generations and humankind, HHGE is not only a scientific, technological, or medical issue, but also a societal and national issue that should have public engagement and obtain public consensus. In a similar vein, when the citizens of a country decide to take the next step to enter into HHGE, the recommendations from an authoritative

international advisory body are indispensable. No scientist, no country can work alone.

*Renzong Qiu, PhD, is professor of Philosophy of Science and Bioethics at the Chinese Academy of Social Sciences in Beijing, China, and a fellow of the Hastings Center.*

## **David Liu** (Broad Institute/HHMI)

### Thoughtful, balanced, and well-bounded

I continue to struggle to image plausible situations in which clinical germline editing provides a path forward to address an unmet medical need that cannot be provided by other options such as preimplantation embryo testing, though I appreciate that opinions will vary on this issue.

Overall, I found the HHGE report to be thoughtful, balanced, and well-bounded. It offers specific recommendations for criteria that would help a proposed clinical germline editing application meet a bar for scientific and medical merit, while acknowledging that societal and ethical merits are not part of the charge behind this report. These boundaries are important, both to recognize stakeholders beyond scientists, doctors, and patients, and to acknowledge that different families, different cultures, and different governing bodies may view certain societal and ethical criteria differently in weighing the potential risks and benefits of clinical germline editing.

"I found the HHGE report to be thoughtful, balanced, and well-bounded"

—David Liu

*David R. Liu, PhD, is director of the Merkin Institute for Transformative Technologies in Healthcare at the Broad Institute and an HHMI Investigator. He is the cofounder of several companies, including Editas Medicine and Beam Therapeutics.*

## **Richard Hynes** (MIT)

### A case for clinical application

This report materially advances consideration of issues surrounding HHGE. The HHGE designation nicely separates the complex issues associated with editing for implantation to produce children with altered genomes from essential research on preimplantation embryos, gametes, and their progenitors, which is necessary to advance understanding of human reproduction.

In line with other recent pronouncements, the report states that there is a case for considering some clinical applications but not until the technology and ethical debate have progressed significantly. The report does not recommend a moratorium on research. Rather, it clearly delineates six categories of potential clinical applications of HHGE and indicates that only two of those could be considered at this time—but only after extensive further research on the efficacy and safety of the scientific methods and broad discussion of the ethics and societal issues raised by HHGE. A pathway for responsible applications of HHGE is clearly described, initially for only the most severe monogenic diseases in a limited number of situations.

Important recommendations include establishment of (1) an international scientific advisory panel (ISAP) as a forum for setting transnational norms to inform decisions by individual states on whether or not to allow HHGE and (2) a mechanism for "whistle-blowing." Although the need for sanctions to be applied in the case of transgressions of regulations is clearly stated, precise mechanisms are not spelled out. This topic needs further discussion; an ongoing WHO committee is considering potential mechanisms for international oversight and regulation.

*Richard O. Hynes, PhD, is the Daniel K. Ludwig Professor of Cancer Research at MIT and a former HHMI investigator. He was co-chair of the 2017 NASEM report on genome editing.*

## **Kiran Musunuru** (University of Pennsylvania School of Medicine)

### Very limited applications for HHGE

In general, I am pleased with this report. I like that it is largely focused on scientific and medical issues, particularly with respect to safety, rather than trying to broadly and shallowly cover all aspects of HHGE for all stakeholders, which was a shortcoming of previous reports. Although I would have preferred an explicit call for a moratorium, the report does enunciate that the serious unsolved safety issues mean that HHGE is nowhere near ready to go forward, under any circumstances.

The detailed analysis of exactly which patients might benefit in the future from HHGE makes it crystal clear that it would be appropriate for very few patients in very limited circumstances. I especially appreciate that the report acknowledges that it will be very challenging to directly edit

human embryos safely and discusses the potential technical advantages of using in vitro stem cell-derived gametes instead—which has not received much discussion but seems to me to be a more realistic way forward in the long run.

*Kiran Musunuru, MD, PhD, is a professor of medicine at the Perelman School of Medicine, University of Pennsylvania; a cofounder of Verve Therapeutics; and the author of* The CRISPR Generation.

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### **Kerry Lynn Macintosh** (Santa Clara University School of Law)

#### Courage and compassion

The International Commission on the Clinical Use of HHGE is to be congratulated on its report describing a translational pathway for correction of mutations that lead to serious monogenic diseases in children. Although the Commission does not render a final judgment on the propriety of clinical uses, it demonstrates courage and compassion by acknowledging the therapeutic potential of HHGE and detailing the elements of safety and efficacy regulation. Alternatives such as bans or moratoria are undesirable and ineffective, because carriers of mutations will circumvent them to get help and have healthy children.[3]

To be sure, regulation must be done in good faith lest it become the practical equivalent of a ban. Likewise, although the Commission recommends that international advisory bodies be consulted, it correctly concludes that the ultimate decision whether to permit clinical uses must rest with individual nations. Difficulty in achieving international consensus in a diverse world should not block access to medical technologies.

*Kerry Lynn Macintosh, JD, is a professor of Law at Santa Clara University and author of* Enhanced Beings.

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### **Eric Meslin** (Council of Canadian Academies)

#### A pragmatic push toward clinical implementation

There are moments in the history of policy debates where science evolves, altering the debate's trajectory, or where new ethical, legal, or social argumentation moves the debate in new directions. For HHGE, there has been no shortage of emerging science and thoughtful argumentation. However, unlike the early debates about somatic versus germline therapy, which drew a bright ''permitted-prohibited'' Maginot line between them, the HHGE discussion has become more nuanced.

The report reflects this emergent nuance, where the focus is not on whether HHGE should be deployed but rather on what the criteria should be for its clinical application, and on what regulatory and oversight conditions must be satisfied to permit its translation from bench to bedside. This is a sensible pragmatic turn for both ethics and regulation of this emerging technology and is clearly a push toward clinical implementation.

No doubt, some will read this as if it is a forgone conclusion that HHGE is both inevitable and desirable. Neither is incontrovertibly true: No technology is inevitable, and desirability is in the eyes of the observer. Indeed, the two assumptions found in the report's summary are significant enough qualifiers to give supporters and skeptics some comfort—''assuming existence of a safe and effective methodology,'' ''assuming analysis of the outcomes of any initial uses did not raise further concerns.'' Both can be read as one chooses, either as unspecified waffling or—as I choose—a set of steps that require societal engagement and tightly constructed testing and clinical introduction protocols.

*Eric M. Meslin, PhD, is president and CEO of the Council of Canadian Academies, founding director of the Indiana University Center for Bioethics, and the former executive director of the National Bioethics Advisory Commission (appointed by President Clinton).*

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## Group II: Societal Issues

### **Hank Greely** (Stanford University)

#### HHGE is ultimately a social question

The HHGE report grew from the aftermath of the He Jiankui fiasco, with its two (subsequently three) ''CRISPR'd babies.'' The Commission tried to describe an appropriate pathway to possible clinical uses of HHGE. It did a good job, with an intelligible, interesting, and useful report. (Shameless self-promotion: Many of its eleven recommendations parallel conclusions in my forthcoming book, *CRISPR People*.)

I have about 10 reactions to the report, but here I want to stress two things. First, the report's most important conclusion is stated clearly, forcefully, and repeatedly: This technology is not ready for use to make human babies. That message is crucial—for the public and for any tempted scientists and governments. But, second, I worry that the report's next most important statement might be overlooked. It acknowledges that the decision to allow HHGE is ultimately a social question, to be decided by countries, not by scientists. Scientific approval

of safety and efficacy is necessary but it is not sufficient. The report makes that point.

I wish it had said that even more clearly and frequently, though I am not confident it could say it blatantly enough to be believed. But that message is crucial, both as a matter of democracy and for the standing of ''Science.'' Science cannot afford to feed the Frankenstein mad scientist myth, the one that He Jiankui reinvigorated. That myth is both wrong and bad for Science. The report takes it on; to switch monsters, I worry it may not have buried it at a crossroads with a stake through its heart.

*Henry T. Greely, JD, is a law professor at Stanford University and the author of* CRISPR People.

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## **Françoise Baylis** (Dalhousie University, Canada)

### Consensus? What consensus?

The authors of the 2020 HHGE report[1] are to be commended not only for clearly outlining how few prospective parents might benefit from HHGE (pp. 112–118) but also (and perhaps more importantly) for appropriately emphasizing the need to involve society in ongoing discussions on the (im)permissibility of HHGE. This is not the sole purview of science; there is much more at stake than safety, efficacy, and effectiveness. To fully appreciate the importance of this contribution to ongoing discussions, a bit of history and context is required.

The Organizing Committee of the 2015 *International Summit on Human Gene Editing*[4] (of which I was a member) called for ''broad societal consensus about the appropriateness of any proposed use of [HHGE].'' It also recommended an ongoing international public forum to ''engage a wide range of perspectives and expertise.'' The Organizing Committee of the 2018 *Second International Summit on Human Genome Editing*[5] endorsed the need ''for an ongoing international forum to foster broad public dialogue,'' but expressly eschewed the call for broad societal consensus.[6] Instead, it affirmed the permissibility of research on HHGE and called for a translational pathway from research to clinical use. The 2020 report is the answer to that call.

Importantly, this report includes multiple references to societal debate, dialogue, discourse, deliberation, public or societal engagement, and societal decision-making. Notably, however, there is no mention of societal consensus.[7–10] This raises important questions: Who decides (and on what basis) that there has been sufficient societal debate, deliberation, and engagement such that it is time for societal decision-making? And if this decision-making is not to be by consensus, how is it to be done?

*Françoise Baylis, PhD, is University Research Professor, Dalhousie University, and the author of* Altered Inheritance.

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## **Laura Hercher** (Sarah Lawrence College)

### Nothing easy about establishing consensus

The NAS/Royal Society commission, like every group who has studied the question of HHGE, believes it should be used only when and if it can be done safely. This is not in dispute. What makes HHGE controversial is that it is easy to imagine both good uses (fixing inborn errors responsible for severe disease) and bad uses (tweaking human brains for greater intelligence, perhaps at the expense of empathy or compassion). For this reason, previous iterations of HHGE guidelines have suggested limiting use to what are defined here as ''serious monogenic diseases.''

The current report breaks new ground in that the authors envision a potential way forward for a ''new class of use.'' This ''responsible translational pathway'' comes with many proposed safeguards, including national and international regulatory bodies. The report stresses the need for ''ongoing discussions'' that would allow a broad cross section of society a voice in determining what uses of HHGE are permissible.

There is nothing easy about establishing a societal consensus on a highly technical and ethically complex topic, and no commentators have offered a detailed blueprint for how such a thing could be achieved. One way to start would be to acknowledge a truth that this report hints at but does not state clearly: For the prevention of severe monogenic disease, we have technologies that are far more promising than HHGE. Those uses will be rare. The unique potential of HHGE is that it can be used to introduce DNA not in the parental germline. We dance around this point way too often, in ways that are misleading to the general public, and compromise any hope of real and informed consensus.

*Laura Hercher, MS, is director of Research at the Joan H. Marks Graduate Program in Human Genetics at Sarah Lawrence College, Bronxville, NY, and host of* ''The Beagle Has Landed'' *podcast.*

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**Dianne Nicol** (University of Tasmania, Australia)

### Ticking the "societal discourse" box

Central to the report's recommendations is a cautious ''amber'' light for HHGE at some future time—but only in situations where (1) it is not otherwise possible to create genetically related offspring free from serious monogenic conditions; (2) a set of onerous criteria are satisfied; and (3) there are assurances of safety, efficacy, and efficiency. Although some might argue this is effectively a red light, such a precautionary approach is entirely appropriate given the issues at stake.

The report also rightly emphasizes the need for national regulation, while not denying the value in developing global governance standards. This makes sense—countries taking the lead in HHGE must have appropriate regulations and regulators in place to ensure that HHGE is only undertaken in a highly regulated environment. Countries such as Australia will likely be followers, as significant legislative reform will be required if there is to be even the slightest prospect of an HHGE green light.

Finally, the report rightly recommends (as many have before) that informed societal debate is an essential precursor to HHGE implementation. Regrettably, though, further guidance and evaluation is considered beyond its scope (a familiar story). Though social dialogue with disease and disability groups, potential recipients, and civil society is appropriately highlighted, more is needed. My colleagues and I recently proposed broader, deeper, and more inclusive forms of citizen deliberation, not just nationally but also globally.[11] This much is needed, at the very least, to avoid simply ticking the ''societal discourse box.''

*Dianne Nicol, PhD, is director of the Centre for Law and Genetics, University of Tasmania, Australia.*

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**Sharon Terry** (Genetic Alliance)

### Discourse and interconnectedness

I am pleased that the report concludes that HHGE is not yet safe or effective enough to be used in human embryos. I think it is right to limit it to the prevention of serious monogenic diseases, if and when it does become safe and effective.

I think the most important statement the Commission made is their call for societal discourse and engagement before any decisions are made. In addition, they made the wise statement that true engagement itself must be something that is studied. This discourse should be led by various stakeholders and not just scientists. A top-down approach to leadership here should not be predominant, and communities must have their own leaders help shape this conversation.

It will be very hard to have this discussion across countries and cultures. Contrasting values, differing priorities, and the tremendous impact of poverty, disparity, and marginalization will challenge the premise on which these discussions will stand. It is essential that grassroots communities and their leaders from around the world participate in local, and eventually, global discussions. This year, we have witnessed our interconnectedness as countries around the world suffer from the pandemic. Even the California wildfires have affected distant countries. Editing the human genome will affect not only all living people but also their descendants. This requires robust and meaningful deliberation.

*Sharon Terry, MA, is president and CEO of the Genetic Alliance nonprofit organization, a theologist by training and a fierce advocate for consumer participation in genetics research.*

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**Gaetan Burgio** (Australian National University)

### Societal aspects missing

The strong point of this thorough report on HHGE is to define a responsible translational path toward HHGE. It establishes very rare instances of clinical indications for HHGE, supports further research, and issues a call for global governance. However, there is a series of major weaknesses and contradictory statements, such as the assertion that HHGE should not occur in places without the necessary expertise or appropriate regulatory framework, whereas HHGE will be most likely to occur in these sorts of places. In addition, the call for global governance is laudable but the proposed implementation is unclear on its positioning among existing entities such as WHO or UNESCO and national sovereignty.

Finally, some important societal aspects—in my view more critical than the focus on the science—such as health inequalities or access to reproductive health, were unfortunately missing from this report. Overall, this report provides a solid scientific ground for HHGE in the benefit-versus-risk perspective but is unfortunately too heavily focused on the science and not enough on important societal issues on reproductive health.

*Gaetan Burgio, MD, PhD, is group leader and genome-editing researcher at the John Curtin School of Medical Research, the Australian National University, in Canberra, Australia.*

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### Samira Kiani (University of Pittsburgh)

#### Call for public debate

The HHGE commission performed an extensive review on different aspects of human germline editing. It concluded that ''unless and until'' this procedure can be done safely, nations should not proceed. The committee delineated what safety means and how it should be defined in the context of HHGE. Although this is an important step to ensure safe translation of the technology to humans, the committee appropriately presumes that some nations will move forward with HHGE at some point. For some practitioners, these recommendations could serve as a ''green light''—once safety is met, then we can move on with HHGE.

I feel this is, indeed, a slippery slope. We do not yet know enough about biology, evolution, and their interactions. How do we want to play the role of ''responsible ancestors'' for future generations? Many genetic disorders might be solved by using somatic gene editing without the risk of introducing intentional changes in the genome; others can be mitigated by transient modulation of gene expression. The focus should be on enabling these applications.

Although HHGE might offer certain advantages in some conditions, delineating pathways to perform it safely should involve society at large, to really understand whether ''we as human beings'' want to create this collective future—to contemplate the risks involved to society and incorporate those measures immediately in these technological decisions. Although we have acknowledged and discussed this need, public deliberation has not been sufficient. This needs to be addressed immediately for us to responsibly move forward with HHGE.

*Samira Kiani, MD, PhD, is an assistant professor in the Department of Medicine at the University of Pittsburgh and a producer of the documentary film project, The Human Game.*

## Group III: The Absence of Ethics

### Arthur Caplan and Carolyn Riley Chapman (NYU Grossman School of Medicine)

#### Pulling the technical cart before the ethical horse

Although broader societal and ethical concerns may have been ''beyond the [HHGE] Commission's charge,''[1] separation of these issues from scientific considerations is deeply problematic. With societal and ethical implications sidelined, the report takes on a decidedly pro-HHGE tone, despite its assertion that the Commission did not make a determination on whether HHGE should be allowed.

According to Recommendation 3 (R3), ''Clinical use of HHGE should proceed incrementally.'' R7 supports research to enable the production of gametes from stem cells, even though in vitro derived gametes raise distinct ethical and societal issues that have not been fully addressed. R10 suggests establishing an international body that can evaluate ''applications of [HHGE] that go beyond the translational pathway defined for initial classes of use of HHGE.'' The report seems to anticipate that HHGE will eventually expand beyond the very limited number of couples that would meet the criteria specified in R4. This stance contrasts with National Academies of Sciences, Engineering, and Medicine's (NASEM's) 2017 recommendation that clinical trials for HHGE should not proceed without the establishment of robust and reliable regulatory mechanisms ''to prevent extension to uses other than preventing a serious disease or condition.''[12]

The new report is a substantial and valuable contribution to the scientific and technical evaluation of HHGE. Nevertheless, shelving broader ethical and societal considerations is not without consequence. As John Evans has cautioned, ''if certain ends or values are assumed, you cannot then have a societal debate about what our collective ends or values should be.''[13] Before considering scientific requirements for an HHGE translational pathway from bench to clinic, we should be having robust debate about whether we even want such a pathway to exist now or in any reasonably foreseeable future. The report, unfortunately, puts the technical cart before the ethical horse.

*Arthur Caplan, PhD, is the Drs. William F. and Virginia Connolly Mitty Professor of Bioethics and Carolyn Riley Chapman, PhD, is a faculty affiliate at the NYU Grossman School of Medicine, New York.*

> "The report, unfortunately, puts the technical cart before the ethical horse."
>
> —Art Caplan and Carolyn Riley Chapman

### Debra Mathews (Johns Hopkins University)

#### Necessary, thoughtful, and incomplete

The report is a critical advance in the international discussion and guidance regarding HHGE; it is clear, detailed, and thoughtful—and it is incomplete. The foreword rightly places the report in the context of the ''twin upheavals'' of the COVID-19 pandemic and social unrest and uprisings in response to systemic racism in policing

and beyond. The past 6 months have brought into sharp relief the inequities baked into many of our societies, and they have highlighted the roles that medical research and care have played in maintaining and exacerbating such inequities.

Although the Commission had a narrow charge focused on defining a responsible clinical translational pathway for HHGE, it was also asked to identify the ''societal and ethical issues [that must be evaluated], where inextricably linked to research and clinical practice.'' Here, the Commission took too narrow a view about what counts as ''inextricably linked,'' focusing primarily on individual benefit and harm from HHGE's use. Early decisions with collective impacts, such as which serious monogenic diseases and pathogenic variants, in whom, will be studied, are no less inextricably linked. They will determine access long before the first patient is in the clinic.

This report was not intended to provide a full accounting of the ethical issues raised by HHGE, and the scientific community is not obligated or well-positioned to fix existing inequities, but we should do our best not to exacerbate those inequities. To do that, we must first broaden our conception of which interests, benefits, and harms count in our evaluation of translational research.

*Debra J.H. Mathews, PhD, is an associate professor and assistant director at the Berman Institute of Bioethics, Johns Hopkins University.*

**John H. Evans** (University of California, San Diego)

## An extremely expensive bridge to a remote island

A few years after the National Academies called for public debate to decide whether to engage in germline modification, which has not yet happened, they now offer a translational pathway all the way to post–World War II reform eugenics. The report is notable for its repeated claim to not have an ethical stance, and calling for society to decide, while clearly having and promoting an ethical stance. For example, their ethics prioritizes satisfying the desire of couples that their children be genetically related over the possible risk to the health of such children. More generally, creating the pathway is like building an extremely expensive bridge to a remote island, using the society's money, and then saying, ''Society can decide to not use it.'' The builders of the report want the pathway to be used, or why would they build it? And, what technologies do they ultimately want?

> "Creating the pathway is like building an extremely expensive bridge to a remote island, using the society's money, and then saying, 'Society can decide to not use it.'"
>
> —John Evans

Given that there are barely enough affected couples on the planet for a trial for their most urgent clinical applications category, presumably the goal is the more controversial applications. It would be better for the public debate if the National Academies described their values and the germline applications they ultimately want.

*John H. Evans, PhD, is the chair-in and associate dean of Social Sciences, University of California San Diego, and the author of* The Human Gene Editing Debate.

**Peter H.R. Mills** (Nuffield Council for Bioethics, United Kingdom)

## Chilling implications

The HHGE report forswears engagement with ''broader social and ethical questions,'' although it recognizes the need to engage with the ethical hurdles that lie along the translational pathway it projects. Indeed, weighing potential benefits and harms lies ''at the heart of the Commission's task.'' Crucially, the potential benefits and harms of HHGE are distributed among different people.

The HHGE does not treat a child; it brings a certain kind of child into existence. So what is relevant about the genetic condition is its tractability to genome editing. It is this, not the seriousness of the disease or disability, that might make monogenic conditions the presumptive initial targets. To be fair, the report recognizes that HHGE is about expanding reproductive choice and not about therapy, but it does not allow this insight to open a reflexive critique of its framing assumptions. As a result, the ethical considerations that inform the report's notion of responsibility (significance of

> "While treating HHGE as a genetic therapy may be morally comforting to its proponents, treating the embryo as if it were a patient may have chilling implications for reproductive rights."
>
> —Peter Mills

benefit and risk) are defined by the assumptions that enframe it (the therapeutic model). Treating HHGE as a genetic therapy may be morally comforting to its proponents, whereas treating the embryo as if it were a patient may have chilling implications for reproductive rights.

*Peter F.R. Mills, PhD, is assistant director at the Nuffield Council on Bioethics, London, the United Kingdom.*

## **Jeantine Lunshof** (Harvard Medical School)

### Hard questions of justification

The HHGE report is an impressive, comprehensive, and detailed guide for the global technology development of HHGE. The commission felt that the ethical, societal, and governance aspects were beyond its mission; however, substantial parts of the report are devoted to outlining the societal dimensions, including governance—national and global. I'll restrict my comments to two issues:

1. Scientific norm-setting: The report lays out criteria for a ''responsible translational pathway.'' Setting and meeting scientific quality standards is a prerequisite for the ethical assessment of any technology and a fortiori for the assessment of translation. Bad science is unethical. However, there is no escape from ''ethics.'' The use of the word ''responsible'' in the report already suggests more than technical quality standards.

On page 159, in the section ''Need for a system of global coordination and collaboration'' the report states: ''There is a collective interest of humanity in the use of a novel technology that can result in heritable changes to the human genome.'' This point stands out from the 158 foregoing pages, as it posits the justification of the whole controversial endeavor in a single sentence. If there was nothing controversial in HHGE technology, the many commissions and their reports would not be needed at all. Even for someone who, like me, has no fundamental moral or philosophical objections to HHGE, this statement is surprising, and is not a compelling argument in any sense.

2. Mitochondrial replacement therapy (MRT): Including references to MRT may seem necessary to present the full spectrum of germline interventions. It is, however, misleading. The societal deliberation around MRT in the United Kingdom is often considered exemplary, which might explain why it is included in this report. But it does not really belong there. The MRT offers a reproductive option in rare cases of mitochondrial diseases. Is a public discussion justified on a topic/therapy that is of vital interest to a handful of individuals? Can the public decide about the ethical permissibility of such therapeutic options?

Referencing the MRT debate raises the question of justification too. What is ultimately at stake? What part of these decision-making processes—the road toward translation—is ethically relevant, for whom, and why? Safeguarding the highest quality standards for any biomedical technology is, indeed, a public interest (and requires very specific expertise). This point is clearly conveyed in the report and rightly taken as a starting point. Intertwining with ethical considerations obscures the hard questions of justification.

*Jeantine E. Lunshof, PhD, is a philosopher and ethicist at the Harvard Wyss Institute for Biologically inspired Engineering, and a lecturer at Harvard Medical School.*

## **LaTasha Hoskins Lee** (National Minority Quality Forum)

### Therapies beyond their reach

I agree with many of the Commission's recommendations and concerns, particularly around the development and use of HHGE and Assisted Reproductive Technology (ART). Strong public policies are needed to ensure equitable access to costly—but potentially curative—gene-based therapies. However, the report lacks diverse patient perspectives. In this new ''CRISPR World,'' issues of equity and ethics must be considered from their point of view.

> "[HHGE] might further expand the divide, where the haves receive editing for chronic illnesses or "designer babies," while the have-nots aren't afforded this privilege."
>
> —LaTasha Hoskins Lee

Sickle cell disease (SCD) is an excellent example of a potential HHGE target with implications for health disparities. Somatic CRISPR-Cas9 gene editing is being used in clinical trials to cure this monogenic disorder. However, new attention from the pharma industry and research organizations has prompted individuals with SCD to express concerns of

future abandonment; that these potentially risky therapies are tested first in SCD to ''figure it out on us, then go to other diseases, leaving us again with no options.'' The SCD patients may not have access to gene-based therapies when costs are no longer covered by the trial sponsor. This vulnerable population may have shouldered the risks of therapies that are still under development, only to find the optimized, approved therapies are beyond their reach, particularly as many SCD individuals are publicly insured in the United States by Medicaid and Medicare.

If HHGE does become safe and legal, it might further expand the divide, where the haves receive editing for chronic illnesses or ''designer babies,'' whereas the have-nots are not afforded this privilege. The question remains: Will we be on the right or wrong side of history 30–50 years from now?

*LaTasha Hoskins Lee, PhD, MPH is vice president of Social and Clinical Research & Development, National Minority Quality Forum, Washington, DC.*

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### **Bryan Cwik** (Portland State University)

#### No ethically neutral discussion

One thing that the saga of the past 5 years (since the first experiments with CRISPR on human embryos) has shown is that speculation about the future development of the technology has been a poor guide to where we appear to be heading. The likely future clinical applications of gene editing in reproductive medicine are far more limited (at least in the near- to medium term) than the decades of speculation about designer babies and the like would have us think. Periodic review of the actual state of translational research is going to be necessary to craft good ethics and regulatory policy. The HHGE Commission's report is necessary and will (I hope) be the first of a set of these reviews.

But one thing this report has reaffirmed, despite the Commission's best efforts, is that there is no ''ethically neutral'' discussion of gene editing. The Commission intended to avoid ethical discussion. But, perhaps without being aware of it, the Commission took a very strong stance on a key ethical issue—clinical justification—when they stated that gene editing should be restricted in the near term to serious, monogenic disorders. Rather than rehash the same tired distinction between the ''ethics'' and ''technical'' issues, it is better to accept that, with gene editing, these are going to have to go hand in hand as we collectively figure out what to do with this potentially disruptive technology.

*Bryan Cwik, PhD, is assistant professor of Philosophy and University Studies at Portland State University.*

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## Group IV: Regulation and Enforcement

### **Robert Cook-Deegan** (Arizona State University)

#### Drafting a regulatory roadmap

The HHGE report makes sensible recommendations about regulation and oversight. It is time to move from drafting reports and guidelines to building a framework to carry out the recommendations from the profusion of reports. Let us hope the forthcoming WHO report marks the transition from talk to action.

Different nations will make different choices, much as they have regarding human embryonic research. Four elements are needed: three in each nation that contemplates HHGE, and the fourth is an international convening function.

1. A credible process for evaluating the evidence of safety and efficacy of proposed interventions (e.g., the FDA). The obvious action in the United States is to remove the Aderholt appropriations rider and convene an advisory body to specify the criteria for evaluating prospects of safety and efficacy. Then, protocols should be reviewed if and when they are ripe.

2. A scientific effort to build the evidence for safety and efficacy. The logical action is to clarify or remove the Dickey-Wicker appropriations rider that hobbles the federal research effort, and to convene a credible advisory committee to guide government research priorities.

3. A systematic process for assessing when societal consensus is sufficient to warrant approval of initial protocols. The NIH nor FDA need to be involved, but neither has sufficient credibility among nontechnical constituencies to mediate a broad public debate or to assess a social consensus. Bioethics commissions have addressed similar questions with mixed results. The alternative is to leave social assessment to political institutions. That leaves a choice between organized and disorganized cacophony. My own preference is for a systematic effort, but with real trepidation about prospects of success.

4. International convening. The 2015 and 2018 genome editing summits and the planned 2021 event are a good start. The report offers OECD, UNESCO, and WHO as possible convenors. International coordination needs a reliable budget and secretariat, but not

necessarily a unitary convenor. The HHGE report wisely refrains from picking a winner, and there need not be any losers if a triennial event budget can be cobbled together.

*Robert Cook-Deegan, MD, is a professor in the School for the Future of Innovation in Society at Arizona State University, and the author of* The Gene Wars.

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**Carolyn Brokowski** (Yale University School of Medicine)

### Regulatory questions abound

The HHGE report successfully raises critical considerations about preclinical safety and efficacy. However, a number of outstanding regulatory and legal questions remain. Several of the Committee's recommendations encourage additional layers of regulatory oversight. Recommendation 9 (R9) is for the establishment of an ISAP ''with clear roles and responsibilities'' regarding data review, preclinical (and perhaps eventually) clinical use, safety, and efficacy of HHGE. R10 notes that an international body with ''diverse expertise and experience'' may define and oversee new classes of use. And R11 holds that there should be an international mechanism to express concerns about possible deviations from established guidelines and where recommended standards could be disseminated to national authorities and the public.

Why, if at all, should any international body have vested authority to advise states and/or make decisions about HHGE? Why should states that already possess sound regulatory structures accept the body's purported authority? Who prevails in cases where there is disagreement between international oversight groups and national regulators? Who might fund ISAP? Will extra layers of oversight deter investigators from engaging in the study of HHGE as the Committee has defined it? Absent recommendations that have been codified into any given national legal structure, how, if at all, could global bodies enforce their guidelines? And for those countries lacking a well-defined regulatory structure in the first place, what incentives might compel international guidance and oversight to be adopted and integrated?

These difficult, technical matters must be addressed if successful international oversight of HHGE is possible.

*Carolyn Brokowski is a doctoral student in emergency medicine at the Yale School of Medicine.*

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**Tetsuya Ishii** (Hokkaido University, Japan)

### Unfinished symphony

The report on HHGE attempted to clarify possible standards for HHGE, should society accept it. Primarily, it proposed applicable cases, such as the risk of passing serious monogenic diseases to offspring (Recommendation 4, R4). Recommendation 8 (R8) stated that clinical ethics, rigorous review, and social discussions and norms are important in each country. R4 and R8 have already been proposed elsewhere.

More importantly, the report discussed ideal genetic modifications—which are potentially hampered by genomic instability or by single-base and meiosis errors in the germline—but offered no possible approaches to achieve such modifications (R5). R6 warned about mosaicism in the cells biopsied for embryo testing and stressed the importance of monitoring pregnancy and offspring after HHGE. But again, the report failed to present ethical approaches for long-term follow-up of offspring, who are unlikely to be informed about HHGE by their parents or can withdraw consent.[14] Moreover, it failed to address pregnancy management strategies, including abortion.

Although there is no medicine without risk, the report does not discuss any clinical and legal issues, including wrongful birth and life lawsuits.[15] Unfortunately, therefore, its mission remains incomplete and unfinished from the perspective of clinical reproductive medicine.

*Tetsuya Ishii, PhD, is a professor in the Office of Health and Safety, Hokkaido University, Japan.*

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**Jacob Sherkow** (University of Illinois)

### Rogues and enforcers

The HHGE report relies, in substantial part, on using law as an instrument of international governance of heritable genome editing. Although this is understandable, actually enforcing such a system—even if well-crafted according the report's principles—will remain particularly fraught in the international context. As noted by Alta Charo, there will always be ''rogues'' under such a system; what should a country do when it catches one of its own?

Enforcing any legal regime that cabins heritable genome editing will require jurisdictions to answer questions such as the bounds of appropriate punishment for illegal genome editing behavior, for example, imprisonment or fines; defining exactly who the ''rogues'' are,

for example, scientists, technicians, or paying patients; and what to do about rehabilitating such actors in the future. Different answers to these questions across jurisdictions may very well regress to the same fractured map of HHGE legality currently in place.

*Jacob S. Sherkow, JD, is a professor of Law at the University of Illinois Urbana-Champaign and an expert on CRISPR patent issues.*

## **Rodolphe Barrangou** (North Carolina State University)

### A critical piece of an incomplete and complex puzzle

Predictably, the consensus report conclusively states that CRISPR/genome editing technology is not ready for HHGE implementation. Besides the technical assessment and stated scope of work, the report does recognize the importance of societal implications, but such an expert and authoritative committee should responsibly encompass a more comprehensive set of voices. At a time where we have an acute appreciation of the need to be diverse and inclusive, we should be ready to complement scientific insights with societal values. Given the perception of the field and the well-documented ethical shortcomings of CRISPR, we should not shy away from ensuring diverse voices are properly accounted for and important concerns thoroughly addressed.

Besides the persuasive recommendations outlined in the report and the science-informed foundation laid out, we should have a greater sense of urgency to encompass ethical, religious, and societal considerations, especially given the pace at which this field is evolving and this technology is spreading. To (re)build and (re)gain confidence in the scientific community, we need to discourage misuse more vehemently, condemn rogue applications, and compel oversight bodies to forcefully monitor users and vigorously enforce guidelines. We need a consensus that extends beyond the scientific realm, so we should not limit the scope of such authoritative reports to scientific opinions.

*Rodolphe Barrangou, PhD, is a distinguished professor at NC State University and a cofounder of several companies, including Intellia Therapeutics and Locus Biosciences.*

## **J. Benjamin Hurlbut** (Arizona State University)

### More opiate than solution

The HHGE Commission's task was to define how to do responsibly what He Jiankui did irresponsibly. It has delivered. Although He, an ambitious young scientist, moved with reckless speed, the Commission has constructed a careful, measured, ''staged rollout,'' overseen by scientific experts and built to hold ''rogue'' actors like He in check. But if He's violation was going out on his own (never mind that numerous prominent scientists encouraged him and multiple powerful Chinese public figures gave him their blessing), the Commission strays into the same dangerous waters, laying claim to questions of responsibility that are not its own to decide.

Indeed, in defining the Commission's charge, the National Academies and Royal Society made the same false assumptions that motivated He's experiment: HHGE is inevitable; the destination is predetermined; if we do not lead the way and write the rules, someone else will.

> "By setting minds at ease, the report is more opiate than solution."
>
> —J. Benjamin Hurlbut

Designing responsible regulation is inseparable from—and necessarily subsidiary to—prior democratic judgments of purpose, social benefit, and public good. The report reverses that relationship, appropriating the authority to say what is responsible. The result is a technocratic protocol that designates ''benefits'' and ''risks,'' but in the face of persistent public uncertainty about what would even qualify as a responsible or beneficial use. It may feel comforting to reduce unprecedented questions of the human future into matters resolvable through familiar regulatory processes. This is false comfort, even as we should be feeling uncomfortable. By setting minds at ease, the report is more opiate than solution.

*J. Benjamin Hurlbut, PhD, is associate professor in the School of Life Sciences at Arizona State University and the author of* Experiments in Democracy: Human Embryo Research and the Politics of Bioethics.

## **Sheetal Soni** (University of KwaZulu-Natal, South Africa)

### Value cultures and traditions in debate

For me, the regulatory approach suggested by this report is interesting. It envisages a dual approach to HHGE.

First, national regulation through law and institutional bodies, and then international oversight through an international panel. This is significant, because the report states that countries should develop their own regulatory approaches. But if we left countries to do this in isolation, you would invariably have some countries that take a very strict approach to the circumstances under which they are willing to permit HHGE, and those who have a more flexible or relaxed approach. Inevitably, this creates the conditions for reproductive tourism, where people will travel to the country where they can obtain the treatment they want.

An international oversight mechanism is a sound recommendation. This is not about hyper-regulation. Countries must be encouraged to drive debate about HHGE, because the global arena is not homogenous. An international body would help us bring our different approaches together and attempt to agree on common values and approaches. Our DNA makes us similar, but our cultures, traditions, and social values make us different. Debate helps us to find common ground on important issues, and HHGE is relevant to every human on the planet.

*Sheetal Soni, PhD, is deputy academic leader for Teaching and Learning and a lecturer in bioethics at the University of KwaZulu-Natal, Pietermaritzburg, South Africa.*

## Group V: Clinical and Technology Considerations

### **George Church** (Harvard Medical School)

#### Germline versus somatic debate

The recent HHGE report follows a well-worn path, warning us about esoteric technologies that we already do not want—egg edits—just as we do not want jetpacks or underwater homes. Meanwhile, the report ignores adjacent technologies that are far more addictive, ''heritable,'' and enhancing. While addressing a life-threatening disease, therapeutic cells can be pathogen/cancer/senescence-resistant to ''do no harm,'' but those same features could be enhancing. As somatic therapies improve for common diseases, these will spread into preventative medicine—with economies of scale, and ever earlier application, including human embryos (without affecting the germline). Ironically, such somatic enhancements can be more ''heritable'' than a rare disease from a homozygote. The latter has close to 0% offspring with the same disease, due to the abundance of normal alleles in the population (and/or genetic counseling), whereas the former can be close to 100% due to the addictive nature of safe and effective technologies.

For germline sensu *stricto*, somatic cell nuclear transfer methods (not mentioned in the HHGE report) are in routine use in animals such as pigs[16] and improving rapidly. Advantages of such germline versus somatic methods include: multiplex editing, clonal checking of genetic and epigenetic precision/non-mosaicism, lower off-target rates due to fewer independent cells, 100% immune tolerance, 100% delivery to every cell, and $0 to subsequent generations. The disadvantages of germline relative to somatic therapies include possibly longer clinical trials (to assess long-term effects) and the smaller impact of a newborn cohort of 10 million/month versus 7.7 billion already alive.

*George M. Church, PhD, is the Robert Winthrop Professor of Genetics at Harvard Medical School, the Wyss Institute, and many others. He is the cofounder of dozens of companies, including Editas Medicine and eGenesis, and the coauthor of* Regenesis.

### **Helen O'Neill** (University College London, United Kingdom)

#### Broad intentions but narrow criteria

The HHGE report begins with broad intention but ends with narrow criteria. Although the regulatory, societal, and ethical issues are inextricably linked to the science and the application of the technology, it is the latter that determines the complexity of the decisions made in the former categories. Put simply, the closer to perfection embryo editing technology gets, the easier it is to disentangle the ethical and legal complexities.

"The [HHGE] report follows a well-worn path, warning us about esoteric technologies that we already don't want—egg edits—just as we don't want jetpacks or underwater homes."

—George Church

There are two problems with this: First, no matter how precise the technology becomes, embryonic development is an imperfect process. Our full understanding of the preimplantation embryo is hampered by limited access to zygotes, and legal constraints pertaining to the creation of embryos for research purposes. Second, speaking broadly is a disservice to the rapid refinements

of the technology and the propensity to which these address individual concerns.

The report relies on traditional and tried arguments to justify lack of support for HHGE without giving deserved attention to the multitude of advancements in both genome editing and ART, which annuls many of the former concerns, especially those regarding DNA repair pathways and embryo testing procedures. For example, there is a dearth of emphasis regarding base editing, which would allay concerns about double-strand break repair and is a more likely candidate for clinical application of HGGE for monogenic disorders. As for the latter, advances in noninvasive testing of culture media could allow for better monitoring of embryos than in the current practice in in vitro fertilization.

*Helen O'Neill, PhD, is a lecturer in Reproductive and Molecular Genetics at University College, London, the United Kingdom.*

## **Lluis Montoliu** (CNB-CSIC, Madrid, Spain)

### A door is dangerously opened

Genome editing could, in principle, be applied on human embryos to fix a mutation and hence permit the birth of a healthy baby. However, the technique is not yet ready to be used safely and robustly, nor was it ready in 2018, when the first three human beings had their genomes edited. This is one of the messages reiterated in the new HHGE report, which builds on the previous document published by the National Academy in 2017 (ref. 12) and uses some concepts available in the 2018 report by the Nuffield Council of Bioethics.[17]

Current genome-editing technologies do not ensure that only the intended changes will occur at the target locus, nor that other alterations might impact other genome locations, as the latest experimental data confirm. Therefore, at present, the clinical use of HHGE techniques is not recommended. However, should our knowledge of genome-editing techniques advance significantly, the report anticipates recommendations to regulate how such experiments could be attempted. It is important to highlight societal and cultural considerations, beyond science, to inform future discussions about HHGE. A door is dangerously opened to consider non-translational applications, which seems premature, particularly when relevant clinical applications are not yet available.

*Lluis Montoliu, PhD, is a professor at CNB-CSIC and CIBERER-ISCIII in Madrid, Spain, and President of ARRIGE.*

## **Bob Williamson** (Murdoch Children's Research Institute, Australia—Retired)

The HHGE report deals with the scientific challenges of using CRISPR to make heritable changes in the DNA of a human embryo, to change a person's phenotype and improve health. It is an excellent report, as far as it goes, but it looks at the issues narrowly when the problems are not narrow but wide. It suggests that gene changes using CRISPR should, at first, be confined to Mendelian diseases. It mentions (but does not underline) the incredible rarity of situations where this may be needed (most couples at risk of having a child with a serious Mendelian disease have the easier, and for most, more ethical option of preimplantation genetic testing).

It is a pity the Commission did not make recommendations on ethics, instead of leaving this to each country, and to the future. An ethics analysis should come first. It was the unethical nature of Dr. He's ''experiment'' in 2018 that called forth condemnation from every major academic body. The Commission could have looked at a real-life issue involving a complex disease, such as the roughly 100 million people worldwide who are homozygous for the allele *APOE4*. Any child of such a person has a greatly increased risk of developing Alzheimer disease, like their parent; that is, 100 million candidates for changing the E4 allele in an embryo or gamete to E2 or E3, with much lower risk. Think of the enormous health and economic benefits from the reduction in the number of people developing dementia. But how do we balance safety, precision medicine, ethics, and charges of eugenics in an important, real-life situation such as this? Or similar situations for coronary artery disease, or some forms of cancer?

So, the report is great science, but the science and the ethical conclusions are interdependent and should be examined together, now.

*Robert Williamson, PhD, is a retired professor of Molecular Genetics at St Mary's Hospital Medical School, Imperial College London, and Murdoch Children's Research Institute, Melbourne, Australia.*

### Robert Ranisch (University of Tübingen, Germany)

#### The translational dilemma of first-in-human

The report fails to acknowledge a dilemma of first-in-human trials: the *translational dilemma*. Any clinical use of HHGE requires ''sufficient preclinical evidence.'' However, to obtain further knowledge ''on the safety and efficacy of the technology,'' clinical trials are eventually unavoidable. A final evaluation cannot be made before attempts to establish a pregnancy. The dilemma is that safety must be guaranteed before the initial clinical use of HHGE, yet it can only be proven after risky experiments.

This situation is not unique to the initial clinical use of HHGE. However, unlike most first-in-human trials, consent cannot be obtained from future children (or even future generations) and safety can only be assessed after long-term monitoring. Crucially, in the case of HHGE a potential patient has been created rather than treated.[18] Possible risks could simply be avoided by refraining from the clinical trial.

Almost 40 years ago, Hans Jonas maintained that future developments in reprogenetics could only be established with a ''trial-and-error approach,'' which, in turn, would render these applications unacceptable, despite potential benefits.[19] If the clinical use of HHGE ever becomes acceptable, the translational dilemma deserves more attention in defining a responsible pathway.

*Robert Ranisch, PhD, is a professor at the International Centre for Ethics in the Sciences and Humanities, University of Tübingen-Wilhelmstr, Germany.*

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### Guillaume Levrier (University Sciences Po, Paris)

The essence of government can be scrutinized through the lens of establishing standards. Being in a society in which people cannot agree on a yardstick to measure distances or are unwilling to submit to consensual mechanisms to resolve disputes is a convincing definition of living under a failed state. In that perspective, establishing new standards can feel like achieving a civilizational purpose. Building a process to standardize variants, a possibility opened by HHGE ''to change a disease-causing allele to a common allele in the population that is known not to cause disease,'' has the texture of an object with anthropological dimensions.

The authors of the HHGE report have tried to shirk from showing any biopolitical intent. Yet in doing so, they might have set impossible standards for many possible variants. The blanket refusal to consider non-homologous end-joining and mosaicism as potentially conferring medical benefits is a blow to future developments. The proposed governance mechanism relies on trust and good faith in a multilateral context: Neither of the governments whose academic institutions hosted this work can be expected to provide any.

This report does level an epistemic landscape. But it will be up to others to decide what should be built in it.

*Guillaume Levrier is a doctoral candidate at University Sciences Po in Paris, writing his thesis on international policy issues raised by genome editing.*

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## And Finally…

### Misha Angrist (Duke University)

#### The HHGE drinking game

Let us play the germline—or if you prefer, ''heritable''—genome editing drinking game. Every time someone writes that term and, within shouting distance, they or any of their co-conspirators write ''ethical,'' take a shot of your favorite adult beverage. ''Commission?'' Take a shot. ''Translational pathway?'' Shot. ''Off-target effects?'' Beer bong (or off-target beer pong!). ''Regulatory,'' ''oversight,'' ''global/international, ''or ''governance?'' One shot each (''expert advisory committee'' merits at least two). By now, we should be well above the legal limit—certainly too hammered to drive home.

Time to sober up. When someone writes ''Somatic genome editing therapies are also likely to be very expensive, although costs are unknown and likely to vary,'' smack yourself across the face and down a shot of espresso. It is now 5 AM and you think you are nearly coherent again. Then you read, ''For individuals with edited genomes who continue to consent to and engage in a monitoring process into their child-bearing years, this process would provide an opportunity to invite these individuals to include any children they have in an intergenerational assessment, thus enabling the follow up of grandchildren bearing an edited genome.''

Alas, it is no use. Go to the bathroom, lean over the porcelain, and purge. Before you pass out, try to remember to open your rideshare app. With any luck, you will wake up in your own bed and forget that any of this ever happened—at least until the next consensus commission report (DRINK!).

*Misha Angrist, PhD, is an associate professor at Duke University, an early participant in the Personal Genome Project, and the author of* Here is a Human Being (2010).

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