CRISPR’d babies: human germline genome editing in the ‘He Jiankui affair’*

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ABSTRACT

The world was shocked in Nov. 25, 2018 by the revelation that He Jiankui had used clustered regularly interspaced short palindromic repeats (‘CRISPR’) to edit embryos—two of which had, sometime in October, become living babies. This article is an effort to provide some deep context for the He Jiankui affair and to begin analyzing it. It focuses on He’s experiment, without delving into the broader ethical issues around ‘human germline genome editing’ in the abstract. It begins by carefully defining ‘human germline genome editing’. It then describes the little we know about the experiment before providing background on CRISPR, the pre-He ethical and legal status of human germline genome editing, and on He himself. The fourth, and longest, section provides a detailed narrative of the revelation of the He experiment and its fallout. The fifth section critiques the experiment, which I believe merits unequivocal condemnation on several grounds. The last section suggests some important immediate reactions, by ‘Science’ and by China.

KEYWORDS: Germline genome editing, assisted reproduction, CRISPR, He Jiankui, ethics, eugenics

* I want to thank, effusively, James Rathmell, Stanford JD and MBA, 2019, for his painstaking, consistent, and excellent help as my research assistant. The final version of this article was submitted on May 22, 2019. The facts and statements in it are, I believe, accurate and up-to-date as of then. Given the interest around this story—and the substantial amount that still remains unknown today, less than six months after the world became aware of the He affair—it is undoubtedly the case that new facts will be revealed, and old facts revised. Caveat lector!

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Dolly the sheep, the world’s first mammal cloned from adult cells was born on July 5, 1996. Her birth was kept secret pending the publication of an article about her in NATURE, which, along with SCIENCE, is one of the world’s two leading scientific journals. On Friday, Feb. 21, 1997, NATURE sent out a press release about its upcoming issue, which included the article on Dolly. Following the usual practice of NATURE and similar journals, the story was embargoed until the following Wednesday afternoon, just before the journal’s Thursday publication. The distribution of the press release under an embargo is intended to allow journalists time to prepare well-researched stories about an article that will give the article, and the journal, some immediate publicity. Journalists are supposed to respect these embargo dates.

But that didn’t happen with Dolly. The LONDON OBSERVER, a British newspaper, ran the story as an exclusive front-page story in its Sunday, Feb. 23 edition. Pretty soon the story was everywhere and about 11:00 that Sunday morning in California, I got an unexpected call from my then-Dean. I didn’t get calls from my Dean very often, let alone on weekends. With excitement in his voice, he said (something like), ‘They’ve cloned a sheep! I thought you should know’. And I knew that things were going to get interesting, though I rightly suspected not necessarily in the way my Dean thought.

On a Sunday over 20 years later, I had a similar shock, though not from my (by then-third successor) Dean. After dinner on Sunday night, Nov. 25, I sat down to my computer and went to Twitter, where I saw various retweets of a post by Antonio Regalado, a reporter with the MIT TECHNOLOGY REVIEW, pushing his new article. It was a scoop (a self-, and accurately-, proclaimed ‘EXCLUSIVE’) about a Chinese scientist who allegedly was trying to use ‘clustered regularly interspaced short palindromic repeats’ (CRISPR) to edit the genomes of embryos and transfer them into women’s uteruses in the hopes that the edited embryos would become babies.

Almost immediately, the ASSOCIATED PRESS released its own story, which, based on several weeks or months of discussions with Dr. He Jiankui, confirmed not only the research effort but said two non-identical twin girls had been born as a result. And at about the same time, a series of videos of Dr. He and one of his associates appeared on YouTube.

Regalado’s story broke about 24 hours before the opening of The Second International Human Genome Editing Summit (the ‘Summit’), held in Hong Kong and organized by the U.S. National Academy of Science, the U.S. National Academy of

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1. Hiram Caton, Selling Dolly: An Ethics Hoax, 10 BIOETHICS RESEARCH NOTES 2 (Jun. 1998), http://www.bioethics.org.au/Resources/Online%20Articles/Opinion%20Pieces/1002%20Selling%20Dolly%20an%20ethics%20hoax.pdf (accessed Jan. 11, 2019).
2. Robin McKie, Scientists clone adult sheep, THE OBSERVER (Feb. 23, 1997), https://www.theguardian.com/uk/1997/feb/23/robinmckie.theobserver (accessed Feb. 25, 2019).
3. I can’t, at this point, be confident of the exact language he used.
4. Antonio Regalado, EXCLUSIVE: Chinese Scientists Are Creating CRISPR Babies, MIT TECH. REV. (Nov. 25, 2018), https://www.technologyreview.com/s/612458/exclusive-chinese-scientists-are-creating-crispr-babies/ (accessed Jan. 11, 2019). Regalado, an aggressive and enterprising reporter, had gotten his scoop by checking out a Chinese website that showed ongoing clinical trials. He found a trial listed that was seeking volunteer couples to help create the first gene-edited babies, babies who would be resistant to HIV infection. Regalado had been following genome editing, and humans genomics more broadly, in China for several years.
5. Marilyn Marchione, Chinese Researcher Claims First Gene-Edited Babies, ASSOCIATED PRESS (Nov. 26, 2018) https://www.apnews.com/4997bb7aa36c45449b488e19ac83e86d (accessed Jan. 11, 2019).
6. First gene-edited babies reported in China, YouTube (Nov. 25, 2018), https://www.youtube.com/watch?v=C9V3mqswbv0 (accessed Feb. 25, 2019).
The He Jiankui affair

Medicine, the Royal Society of the United Kingdom, and the Academy of Sciences of Hong Kong. He Jiankui had long been invited to talk at the three-day meeting, though none of organizers seems to have known about his claim to have CRISPR’d babies until the previous week. It was immediately clear that his story would dominate the Summit and its coverage.

Again, I knew that things were about to get interesting. And I was right.

This article is a reaction to the He Jiankui fiasco (the best noun I can think of to describe it). He’s experiment was a reckless ethical disaster — though, we can only hope, not a medical disaster for the babies and their parents. Some rapid responses are critical.

The article starts by summarizing what we know — or, at least, what we have been told — about He’s experiment. It then reverses direction to provide some background about CRISPRing humans, the ethical discussions before Nov. 2018, and the legal status of that work. Next, it walks through the unfolding events around the revelation of He’s actions, before assessing He’s actions. It ends by recommending several short-term responses — by ‘Science’ and by governments — in light of the fiasco.

But before all that, we will start with a note on definitions and context.

I. WHAT IS ‘HUMAN GERMLINE GENOME EDITING’?

This topic is rife with jargon. I want to use this section to clarify what we mean when we talk about ‘He’s experiment’, and especially the phrase I will generally use to describe it: ‘human germline genome editing’.

We can start with ‘human’. Obviously, it means something that is not a monkey, a mouse, a worm, or biological material taken from any of them. But there is a more limited meaning to it in this context. We will use ‘human’ to mean not just that the DNA being modified is from (or in) human cells, but that it is being so modified in an effort to create a ‘human person’. People are, appropriately, much less concerned about modifying isolated human DNA or human cells than they are modifying DNA that is intended to be used in making a baby. Between cells and babies lie embryos that are not intended for use in making babies — embryos that are intended only for research and will never be in a woman’s uterus (‘inside the living’ or in vivo) but only in laboratory equipment (‘outside the living’, or ex vivo, or, alternatively, ‘in glass’, in vitro, these days encompassing a wide range of plastics and other materials). Although different people put different levels of moral value on ex vivo human embryos, what is important in this article is that He’s experiment was on an embryo that was intended to create a human.

So far so good. Then what is a ‘germline’ and why is it important? In short: germline editing creates changes that a person’s descendants can inherit, as opposed to changes that could not be passed on to future generations.

Dr. He used CRISPR to attempt a specific change in the DNA of human embryos, a change that would affect both copies of a gene named CCR5 (named for the protein it encodes, the C-C chemokine receptor type 5, almost always shortened to CCR5, without italics — italics are for genes, non-italics for proteins). By making this change, He

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7 National Academies of Sciences, Engineering, and Medicine, Second International Summit on Human Genome Editing: Continuing the Global Discussion: Proceedings of a Workshop in Brief (Washington, DC, The National Academies Press: 2019), https://doi.org/10.17226/25343.

8 Dr. He calls his work a ‘clinical trial’. Sometimes it is referred to as a ‘study’. I prefer to call it an ‘experiment’. As a clinical trial and as a study it has many shortcomings. It also has shortcomings as an ‘experiment’, but I think that term carries a connotation of uncertainty and risk that is fully appropriate here.
hoped HIV would be unable to infect the white blood cells of the babies born from the embryos. The edited version of the CCR5 gene might be passed down to those babies' children (if any) and might be passed down to their grandchildren, great-grandchildren, and on down the generations. A grandchild could either inherit the edited copy of the gene that came from the grandmother who had been one of the two babies, or the unedited version from that woman’s mate.

This possibility (though not certainty) of intentionally altering descendants’ genes is what most upsets many people when it comes to editing the genes of early-stage embryos. By changing an early embryo, the method seeks to change every cell in any resulting child. Most of a person’s cells are body cells that die naturally during the person’s lifetime or, at longest, survive until the person’s death. These are called ‘somatic’ cells, from ‘soma’, the Greek word for body. But we have cells that have the potential to escape our bodies—and our deaths—by creating a new generation. These cells are our sperm and eggs, collectively known as ‘germ’ cells (from the Latin word for offshoot, bud, sprout, which in middle French came to include ‘seed’) or as ‘gametes’ (from the Greek words for husband and wife, in turn derived from gamos for marriage). Germ cells, and the cells that give rise to germ cells, are called the ‘germline’.

If He Jiankui had edited the ‘somatic cells’ of the twin girls, say by knocking out good copies of CCR5 in the blood forming stem cells of their bone marrow, the children might (or might not—see Section V(B) below) have been protected from HIV infection, but natural reproduction could not pass those changes on to their children. The changes would not have been made in the girls’ eggs. That’s the key difference in editing germline cells instead of somatic ones.

And this ultimately is why I write of germline editing rather than embryo editing. If you edit all the cells of an early embryo, you are necessarily editing both somatic cells and germline cells (or, if early enough, the cells that will eventually give rise to both of those categories). That is why early-stage embryo editing is germline editing, but not all embryo editing will be germline editing. In a later-stage embryo, one might edit selectively only the cells that have already been differentiated along a path that means they could not become germline cells. That would be embryo editing, but not germline editing.

The same idea applies even more to editing genes during a person’s life in particular tissues or organs (apart from ovaries and testes) in order to treat or prevent disease. This concept, called ‘gene therapy’, is gene (or genome) editing but of the somatic cells rather than the germ cells: human somatic genome editing, rather than human germline genome editing. It is likely to be the most important use of human genome editing, but it is not this paper’s concern.

On the other hand, not all human germline genome editing must be embryo editing. One could take eggs and sperm from people and, ex vivo, edit them before using these edited gametes to create an embryo, rather than edit the embryo itself. But one could also edit the germline by putting the editing factors into living babies, adolescents, or

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9 Jacob Sherkow, Patricia Zettler, and Henry Greely, Is it ‘gene therapy’?, J.L. BIOSCIENCES, Advance Access Publication (Aug. 2018), https://academic.oup.com/jlb/advance-article/doi/10.1093/jlb/lsy020/5078563 (accessed Feb. 26, 2019).

10 I suspect that is actually how this kind of editing would eventually be done in order to avoid one of the problems He Jiankui’s efforts encountered – mosaicism.
adults (in vivo) as well as in petri dishes. If you edit the genome of the eggs of 20-year-old women or the sperm-forming cells of 20-year-old men, you edit their germlines.\textsuperscript{11} You might do that by injecting the editing agent into the ovaries or testes. Or you might do that by providing gene editing treatments to a person with a genetic disease, if those treatments ended up editing not only the organs most directly involved in the disease but also, unintentionally and possibly unknowingly, the person’s eggs and sperm. For the purposes of this paper, I will include modifications of the DNA of germline cells when I talk of ‘human germline genome editing’, but I will ignore (almost) entirely the unintended changes to eggs or sperm from what was intended as somatic cell genome editing, because it would be an unintended complication that could and should be monitored and avoided.

I speak of ‘genome’ editing and not ‘gene’ editing because such modifications may often change more than one gene, or even change DNA that is not in what is usually considered a ‘gene’. The ‘genome’ is all of the DNA sequence in a person—the 6.4 billion base pairs in the 46 chromosomes found in the cell’s nucleus as well as the 16,000 or so base pairs found in the DNA of the cells’ mitochondria. To be sure, the particular example of He’s experiment—editing CCR5—targeted one specific gene and could be considered ‘genetic editing’. But some of the proposed uses for germline editing—including their most controversial enhancement uses—will require changes to many pieces of DNA, some in genes and some not.

And, finally, I speak of ‘editing’ for two reasons. First, editing is a technique used to make a specific intentional change: that is, to change an A to a G, to delete a particular stretch of 32 bases, or what-have-you. This distinguishes it from ‘changing’ or ‘mutating’ (just a fancy Latinate word for changing). Second, editing need not be ‘CRISPRing’, because not all gene edits today need to use CRISPR. There are other, older methods—which, though more expensive, time-consuming, and difficult, can also be used to edit DNA. TALENs and Zinc Finger Nucleases are the two most significant. More importantly, we should fully expect new methods, refinements upon, or replacements for CRISPR to appear. When referring to CRISPR as a specific technique, I may use ‘germline CRISPR’ or even ‘CRISPR’d babies’.

What about all of the variations on ‘human germline genome editing’ that appear in scientific publications and the popular press? Sometimes you will read about ‘human genome editing’ rather than ‘germline genome editing’. That is a fair use if the user intends to include somatic cell editing and germline editing, as in a report by the U.S. National Academies of Sciences (NAS) and of Medicine (NAM), and in the Hong Kong Summit that led to the revelation of He’s experiment. You may read about human germline ‘gene editing’ as well as human germline ‘genome editing’. This is usually just a short-cut that saves headline writers a few characters. You may also read about human germline ‘DNA’ editing, which is not significantly different from ‘genome’ editing; it just doesn’t sound as good. And, finally, you may read of human germline genome (or gene or DNA) ‘CRISPRing’ because that is the best technology at our disposal today. But not, perhaps, tomorrow.

\textsuperscript{11} Men continue to make new supplies of sperm from sperm-precursors cells from puberty until their deaths. The consensus (but not unanimous) view is that women, on the other hand, actually make all their eggs before they are born but recruit some to maturity each month during their fertile years.
So that’s our subject: ‘human germline genome editing’, meaning to make intentional changes to DNA of the germline cells of the genome of someone who is, or is hoped to become, a human person. In general, this is what He claims to have done. Let us now turn to the specifics of what we know about his experiment.

II. WHAT WAS THE HE EXPERIMENT?
The only honest answer is ‘we don’t really know’. We have sparse detail and very little information. And none of that information comes from fully reliable sources. Almost all of it is from He himself; a little bit is from a Chinese government news agency’s very short story on a Chinese province’s report on the scandal, a source less suspect that He himself but, as with any government’s report, not fully reliable; and a final little bit comes also from the reports of a handful of American scientists with whom He was periodically in contact.

Here is the story we have been told.

At least as early as 2016, He began experimenting with CRISPR to edit embryos of rodents, monkeys, and humans. Some of the rodent and monkey embryos were transferred into females and led to live births. The human work, at least at this point, was solely on embryos that were not transferred for possible birth. He reported on some of this work at a Cold Spring Harbor Laboratories meeting in Aug. 2017, though it was not (and has not yet been) published.

Sometime in late 2017 or early 2018, He began an effort to produce human babies from gene-edited embryos. Through a Beijing-based organization intended to help Chinese people with HIV, he recruited couples for the experiment, couples where the father was HIV-positive, and the mother was not. Eight couples agreed to participate, although one subsequently withdrew. Of the remaining seven couples, five women had a total of 13 embryos transferred for implantation, two of whom got pregnant. By early Apr. 2018, He reported to another scientist that the one of the women was pregnant with twins. According to the WALL STREET JOURNAL, ‘One October evening, the twins’ expectant father called a member of Dr. He’s lab to say his wife was going into labor. Dr. He raced to Shenzhen airport, postdoctoral students in tow, and flew north’. The woman gave birth that night by emergency cesarean section to non-identical twin girls, who He called, in his statements, by the pseudonyms Nana and Lulu. The site of the birth has not been disclosed, although the fact that Dr. He, located in Southern China, flew north for the birth is some clue. All we know about the second pregnancy is that He characterized it, in late November, as being at a very early stage.

Although Nana and Lulu were born prematurely by emergency C-section, according to He’s late November statements, the girls were healthy by late November when He spoke about them on stage. While still embryos, they had been injected with a CRISPR construct that was intended to cause a 32-base-pair deletion in a gene called CCR5, which is found on chromosome 3. (The version of the gene with this deletion is

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12 This, and some of the other details around the birth, did not become known until May 2019, when published in Preetika Rana, How a Scientist Broke the Rules to Create the First Gene-Edited Baby, WALL ST. J. (May 11, 2019, A1), https://www.wsj.com/articles/how-a-chinese-scientist-broke-the-rules-to-create-the-first-gene-edited-babies-11557506697 (accessed May 18, 2019).
13 Belluck, infra note 114.
14 Rana, supra note 12.
15 Id.
called CCR5Δ32.) This deletion would make the gene produce non-functional copies of the CCR5 protein. Almost all humans have two proper copies of the CCR5 gene, one each on the copies of chromosome 3 they inherit from their mothers and their fathers. A few, especially in Northern Europe, carry one proper copy and one copy of the CCR5Δ32 variant, with the 32-base-pair deletion. And very few humans, again most often in Northern Europe, are known to carry two copies of the mutant gene variation. We do not know exactly all the things the normal CCR5 protein does, except that this protein is found on the surfaces of T-cells, which are white blood cells in the immune system. (There is also some evidence that CCR5 is involved in the brain.) It seems that the most common variety of HIV usually needs functioning CCR5 proteins in order to invade and infect those cells. It was therefore thought that people without any functioning CCR5 genes could not have their T-cells infected with HIV and thus could not contract AIDS. This turns out not to be true, as discussed in Section V(B) below.

Dr. He said his experiment sought to produce humans who, because they had the 32-base-pair deletion that led to a non-functional CCR5 protein, could not contract AIDS.16 However, according to the ASSOCIATED PRESS article, and to data He presented at the Summit, one of the twins was a heterozygote—that is, the CRISPR construct in her cells modified only one of the two chromosomes, which meant that this twin’s T-cells would all express CCR5 protein, though perhaps in reduced amounts. The CCR5 genes on both the chromosomes of the other twin were altered, just not in the way that He planned.

In both twins, some of cells had modified CCR5 genes (one copy for one twin, both copies for the other) while other cells did not. They are what geneticists call ‘mosaics’, people with cells that have somewhat different DNA. And for neither twin did the CRISPR construct do exactly what it was intended to do: cause that deletion of a specific string of 32 base pairs, resulting in the CCR5Δ32 found naturally in some humans. Instead, it made several changes in the twins’ CCR5 genes, changes that apparently would lead to the production of non-functional protein, but changes that had never been seen in humans before. At the same time, He reported that the CRISPR construct had not altered any of the other genes of the babies.

And that is it, everything we have been told. Almost all of the information above comes, directly or indirectly, from He. For his early work with non-humans and with ex vivo human embryos, we have what He said in a talk at a Cold Spring Harbor Laboratory meeting in July 2017—work that has not been published. His talk at the meeting is available on YouTube.17

16 Some have argued that it may have had a cognitive enhancing goal, Antonio Regalado, China’s CRISPR twins might have had their brains inadvertently enhanced, MIT TECH. REV (Feb. 21, 2019), https://www.technologyreview.com/s/612997/the-crispr-twins-had-their-brains-altered/ (accessed Mar. 12, 2019). I think this is unlikely. The evidence for cognitive enhancement is much weaker than the evidence for HIV protection, both in terms of its credibility and the extent of any benefit. Besides, the prospect of HIV prevention both got him his volunteer parents and aligned him with some other scientists, notably Harvard’s George Church, who were pushing human germline genome editing for disease immunity, a position somewhere between straight disease prevention and enhancement. People from He’s labs had contacted scientists who had worked on CCR5’s role in HIV, as well as the role of another gene, PCSK9, in heart disease. He did not contact the groups that had worked on cognitive issues associated with CCR5, and specifically stated that he was against gene editing for enhancement when questioned about this at the Summit.

17 Jiankui He talking about human genome editing, YouTube (Jul. 29, 2017), https://www.youtube.com/watch?v=llxNRMzxyCc (accessed Feb. 26, 2019).
On Nov. 8, 2018, He submitted an application about the experiment to the World Health Organization’s (WHO) Chinese Clinical Trial Registry (ChiCTR), likely in order to make any papers he submitted more publishable in the eyes of scientific journals.18 He updated the application on Nov. 30, but the application was rejected for failure to provide the participant data on safety and validity.19 This ChiCTR posting led Regalado of MIT TECHNOLOGY REVIEW to He’s work.20 Informed consent documents were at one point available in Chinese and English on the website of He’s university, Shenzen’s Southern University of Science and Technology (SUSTC).21 However, the informed consents—along with He’s faculty page and all of the SUSTC pages related to his research—have been taken down.22 In any event, the documents appear to have been woefully inadequate based on the reports of those who read them.23 SUSTC denied any knowledge of the experiments, and the University dismissed He in Jan. 2019.24

On the human baby experiment itself, He spoke substantively in four videos released on Nov. 25, while another video, released at the same time, is an explanation of gene surgery in embryos given by Qin Jinzhou, the embryologist with whom He worked.25 At about the same time that Sunday evening (I cannot tell which happened first), the ASSOCIATED PRESS released a 1700 word story on He’s work, clearly based on many days of speaking with him and his colleagues.26 That story also quotes Dr. Qiu, as well as Michael Deem, a professor at Rice University who had been He’s Ph.D. advisor, and who said he worked with He on the experiment.27

Three days later, on Wednesday, Nov. 28, He gave a 20-minute presentation to the Second International Human Genome Editing Summit in Hong Kong, and briefly

18 Daniela Wei, China Gene-Editing Scientist’s Project Rejected For WHO Database, BLOOMBERG (Dec. 10, 2018), https://www.bloomberg.com/news/articles/2018-12-10/gene-scientist-s-project-rejected-for-whos-clinical-database (accessed Feb. 26, 2019). As of Feb. 26, 2019, the original application is still on ChiCTR’s website at http://www.chictr.org.cn/showproj.aspx?proj=32758.

19 Sheldon Krimsky, Ten ways in which He Jiankui violated ethics, NATURE BIOTECH. 37 (Jan. 2019), https://www.nature.com/articles/nbt.4337 (accessed Feb. 26, 2019).

20 Regalado, supra note 4.

21 Originally available at http://www.sustc-genome.org.cn/source/pdf/Informed-consent-women-English.pdf. Thanks to the ‘Wayback Machine’, a copy of what purports to be an English translation of the consent form of the women (not as far as I can tell for the men) is available on a web archive at http://web.archive.org/web/20181126212007/http:/www.sustc-genome.org.cn/source/pdf/Informed-consent-women-English.pdf.

22 Originally available at http://www.sustc-genome.org.cn/ . As Feb. 26, 2019, the site is inaccessible.

23 Krimsky, supra note 19 (“The informed consent form that he submitted to his research subjects was a 23-page document. It contained many technical terms, had no discussion about the meaning and significance of off-target effects or undesirable on-target changes on the child, and protected his team from responsibility for unforeseen risks. It also failed to inform the parents of alternative methods of preventing HIV infection. There was no evidence that the university or a government ethics body reviewed and approved the informed consent form”).

24 Eli Meixler, Chinese University Fires Scientist Who Claimed to Have Created the First Gene-Edited Babies, TIME (Jan. 22, 2019), http://time.com/5509239/china-university-fires-he-jiankui-gene-editing/ (accessed Feb. 26, 2019).

25 Gene Surgery in Embryos: An Embryologist Explains How It Works, YouTube (Nov. 25, 2018), https://www.youtube.com/watch?v=-1mvZUXgNI (accessed Feb. 26, 2019).

26 First gene-edited babies reported in China, YouTube (Nov 25, 2018), https://www.youtube.com/watch?v=C9V3mqswbvo (accessed Feb. 26, 2019).

27 Marilyn Marchione, Gene-edited baby claim by Chinese scientist sparks outrage, ASSOCIATED PRESS (Nov. 26, 2018), https://www.apnews.com/45ae0c2b522cc488fbb4be777dfc7e95a (accessed Feb. 26, 2019).
answered questions.\textsuperscript{28} He has made no substantive public statements since then. Sometime in early November, He submitted an article describing his study, co-authored by Deem, to \textit{Nature}, which rejected it.\textsuperscript{29} That article is not publicly available, although some people who have read it have spoken to the press. In the ensuring months, a few academics from outside China have spoken about what He had told them before his announcement.\textsuperscript{30}

To that point, everything we have been told about the experiment comes from He, or from a few people working for him or who had talked with him. That information cannot be taken as fully reliable.

On Jan. 21, 2019, the Xinhua News Service, the press agency of the Chinese government, published 350-word article in English that reported on the results of an investigation of He’s experiment by authorities in the province of Guangdong, where the work had taken place.\textsuperscript{31} The Xinhua story did say that the twins existed, that their health statuses, as well as the health of the other pregnant woman, were being monitored, and that He as well as ‘other relevant personnel and organizations’ would ‘receive punishment according to laws and regulations’.\textsuperscript{32} The report itself has not been released. Without casting any particular aspersions of the governments of Guangdong or China more broadly, I think we cannot necessarily take those statements at face value, as those governments have their own perceived interests to protect. For example, STAT recently reported that He may have relied on government funding for his experiment, which the government bodies have largely denied.\textsuperscript{33}

And that’s basically it. We have no corroboration from people outside He’s group or the short news release on the Guangdong investigation about what He did, including whether the babies were gene-edited or, indeed, whether they really exist. We have no independent analyses of the DNA from the babies. We have no outside information about the prospective parents who allegedly let their embryos be gene-edited, and what they were told. We have no clear information (except from He) about the roles played by SUSTC, or by the hospital in whose fertility department the embryos were allegedly edited, and whose ethics committee supposedly approved the experiment.

The paucity of sources does not mean that He’s claims are false. In fact, I suspect most of them are true, if only because if he had truly made up the results, he would have made up better ones. But it is worth keeping in mind.

\textsuperscript{28} https://livestream.com/NASEM/events/8464254/videos/184103056 (accessed Feb. 26, 2019).

\textsuperscript{29} Jane Qiu, \textit{American scientist played more active role in ‘CRISPR babies’ project than previously known}, STAT (Jan. 31, 2019), https://www.statnews.com/2019/01/31/crispr-babies-michael-deem-rice-he-jiankui/?ga=2.109532678.2070114259.1551254097-2104796637.1551254097 (accessed Feb. 26, 2019); Sharon Begley, \textit{Ethical issues plagued newly surfaced paper by ‘CRISPR babies’ scientist}, STAT (Dec. 10, 2018), https://www.statnews.com/2018/12/10/crispr-babies-scientists-paper-rejected/ (accessed Feb. 26, 2019).

\textsuperscript{30} For instance, I spoke on a panel with Dr. Matt Porteus and Dr. William Hurlbut in mid-Jan. 2019. Both were in communication with He before, during, and after his experiment, which they discouraged beforehand and denounced after the revelations in Hong Kong. CRISPR’d Babies – A Discussion with Matt Porteus, YouTube (Feb. 7, 2019), https://www.youtube.com/watch?v=DB65Qsp6ZO (accessed Feb. 27, 2019).

\textsuperscript{31} Guangdong releases preliminary investigation result of gene-edited babies, Xinhuanet (Jan. 21, 2019), http://www.xinhuanet.com/english/2019-01/21/c_137762492.htm (accessed Feb. 27, 2019).

\textsuperscript{32} Id.

\textsuperscript{33} Jane Qiu, \textit{Chinese government funding may have been used for ‘CRISPR babies’ project, documents suggest}, STAT (Feb. 25, 2019), https://www.statnews.com/2019/02/25/crispr-babies-study-china-government-funding/ (accessed Feb. 27, 2019).
But let us now go backward to learn more about CRISPR; about the discussions around the ethical and legal status of human germline genome editing using CRISPR before He’s revelation; and a little bit about He himself.

III. CRISPR, THE ETHICS AND LAW OF EDITED BABIES, AND HE JIANKUI

A. CRISPR

CRISPR stands for ‘clustered regularly interspaced short palindromic repeats’—a name that clearly benefits from its acronym. In one meaning, CRISPR refers to a kind of molecular construct bacteria use to defend themselves from viral invaders. In this sense, CRISPR goes back billions of years—perhaps three billion or more. Humans first began to notice it in the early 1990s. Various scientists, most notably Spanish researcher Francisco Mojica, saw odd debris inside bacterial cells. Mojica and his collaborator Ruud Jansen coined the term CRISPR in an article in the early 2000s. (I do not know whether he was moved at all by the good sound of the acronym in English). Around 2005, Mojica and others realized that CRISPR was actually a bacterial defense mechanism—used, first to recognize, and then to slice up, an invading virus’s DNA (or sometimes RNA). It turns out that many different bacteria have CRISPR systems, systems that use the CRISPR construct in conjunction with various proteins to do their work.

Basically, the CRISPR construct is a homing mechanism. It is made up in part of a protein molecule, and in part of a ‘guide RNA’ molecule. The guide is a perfect complement to a stretch of the virus’s DNA. Thus, if the viral genome has a stretch of nucleotides (the building blocks of both DNA and RNA) that read ATTTGGGCAC, the guide RNA will have the nucleotides that attach to that particular sequence of A’s, C’s, G’s, and T’s. These correspondences are A to U, C to G, G to C, and T to A. (RNA has ‘uracil’, or U, as a fourth nucleotide base, in place of DNA’s ‘thymine’, or T.) In this case, the guide RNA sequence will be UAAACCGUG.

The ‘guide RNA’ finds its complement among the specific sequence of DNA bases in an invading virus’s genome, and the rest of the CRISPR construct holds it tight. At that point, an associated protein becomes involved to cut the grasped DNA totally—across not just one strand of its ‘double helix’, but both—in that specific spot. With its DNA cut, the virus cannot use the bacterial cell to reproduce itself, and its threat ends.

Various proteins have been found that can perform the slicing. The first discovered one that turned out to be important was the not-so-cleverly named ‘CRISPR-associated protein #9’—abbreviated to Cas9—but others exist. The bacterium will produce

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34 A good source for an understandable description of CRISPR and a history of its discovery and development can be found in Jennifer A. Doudna and Samuel H. Sternberg, *A Crack in Creation: Gene Editing and the Unthinkable Power to Control Evolution* (Houghton Mifflin, New York: 2017). Doudna is widely accepted as one of the crucial (non-bacterial) inventors of CRISPR; Sternberg was her graduate student.

35 The Broad Institute, *CRISPR Timeline*, https://www.broadinstitute.org/what-broad/areas-focus/project-spotlight/crispr-timeline (accessed Feb. 27, 2019).

36 Id.

37 Francisco Mojica, César Diez-Villaseñor, Jesús García-Martínez, and Elena Soraia, *Intervening Sequences of Regularly Spaced Prokaryotic Repeats Derive from Foreign Genetic Elements*, 60 J. MOLECULAR EVOLUTION 174 (2005).
various ‘guide RNAs’ based on the genomes of the viruses that invade it and those will stay inside it, as a kind of memory of the past invasion.

Through first decade of the 21st century, Mojica and others—including scientists working for Danisco, the company that makes Dannon yogurt—explored CRISPR as a fascinating piece of natural history: an unexpected way for bacteria, which, unlike humans and other mammals, lack a classical immune system, to defend themselves from pathogens. It was not until 2012 that CRISPR, and especially CRISPR-Cas9, began to be seen as a tool for humans.

The first publication of that idea was by Jennifer Doudna of the University of California, Berkeley, and Emmanuelle Charpentier, a European researcher born in France who, from 2009 to 2014, was a faculty member of Umea University in Sweden. In early June 2012, Doudna and Charpentier submitted an article to the journal SCIENCE on how humans could use CRISPR-Cas9 cut DNA reliably in cells at very specific locations, determined by the guide RNA one added to the CRISPR complex. SCIENCE recognized the importance of the article and published it on-line on June 27, with paper publication following on Aug. 17. As the last line of the abstract of their paper says: ‘Our study reveals a family of endonucleases that use dual-RNAs for site-specific DNA cleavage and highlights the potential to exploit the system for RNA-programmable genome editing’.39

As is often common in science when the time is right, others had similar ideas. Virginijus Šikšnys at Vilnius University in Lithuania submitted an article with similar findings to the journal PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES (PNAS) in May 2012. PNAS put the paper through a peer review process that resulted in questions and substantial back and forth between the editors and the authors. That paper was ultimately published in Sept. 2012.41

Additional important papers were published in Jan. 2013 in SCIENCE. Feng Zhang from the Broad Institute (a collaboration between Harvard University and the Massachusetts Institute of Technology) showed that CRISPR could work not just in the bacterial cells that Doudna and Charpentier had described, but also in the cells of the more complicated life forms called ‘eukaryotes’ that include fungi, plants, and animals.42 George Church, at Harvard Medical School, showed that it could be used to cut DNA in the cells of one particular kind of eukaryote—humans.43

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38 Martin Jinek, Krzysztof Chylinski, Ines Fonfara, Michael Hauer, Jennifer Doudna, and Emmanuelle Charpentier, A Programmable Dual-RNA-Guided DNA Endonuclease in Adaptive Bacterial Immunity, 337 SCIENCE 816 (Aug. 2012).

39 Id.

40 Sarah Zhang, The Battle Over Genome Editing Gets Science All Wrong, WIRED (Oct. 4, 2015), https://www.wired.com/2015/10/battle-genome-editing-gets-science-wrong/ (accessed Feb. 27, 2019).

41 Giedrius Gasiunas, Rodolphe Barrangou, Philippe Horvath, and Virginijus Šikšnys, Cas9–crRNA ribonucleoprotein complex mediates specific DNA cleavage for adaptive immunity in bacteria, 109 PROC. NAT’L ACAD. SCI. 39 (Sep. 2012). The Doudna and Charpentier work did feature an important improvement on what Šikšnys described. Bacteria deploy two different and physically separate kinds of RNA (called a tracrRNA and a crRNA) to use CRISPR; Doudna and Charpentier showed how those two RNAs could be efficiently combined into one construct; Šikšnys did not describe the tracrRNA.

42 Le Cong, F. Ann Ran, David Cox, Shuailiang Lin, Robert Barretto, Naomi Habib, Patrick D. Hsu, Xuebing Wu, Wenyan Jiang, Luciano A. Marraffini, and Feng Zhang, Multiplex Genome Engineering Using CRISPR/Cas Systems, 339 SCIENCE 819, 823 (Feb. 2013).

43 Prashant Mali, Luhan Yang, Kevin M. Esvelt, John Aach, Marc Guell, James E. DiCarlo, Julie E. Norville, and George M. Church, RNA-Guided Human Genome Engineering via Cas9, 339 SCIENCE 823, 826 (Feb. 2013).
The early uses of CRISPR were as scissors, but these and other scientists also figured out how to use them, not just to cut out stretches of DNA, but to replace them with other (human-chosen or human-engineered) stretches of DNA. If a different piece of DNA is present when CRISPR, with any of a number of associated proteins, makes a cut in both strands of DNA, this other piece of DNA will often fill the newly-created gap.

The almost irresistible analogy for anyone writing about CRISPR is the cut-and-paste functions in work processors, particularly Microsoft Word and its ‘replace’ function. With Word you can tell your computer to find any set of characters in a document (say ‘Greeley’), cut it out, and replace it with something else (like ‘Greely’). In cells, the guide RNA in the CRISPR could be chosen to find a stretch of DNA that reads GTG-CACCTGACTCCTGTG. The associated proteins would cut out these 24 nucleoside bases, but the whole complex could include a different stretch of 24 bases, say GTG-CACCTGACTCCTGAG, identical except for the next-to-last nucleotide base, which has changed from a ‘T’ (thymine) to an ‘A’ (adenosine). The new DNA would take the place of the old DNA, and permanently changing the cell’s DNA.

This is not a random example. That stretch of DNA is the first 24 bases found in the gene that makes the beta chain of the protein hemoglobin in some people. People who have two copies of that version (‘allele’) of the gene will develop sickle-cell disease. The proposed change, with the penultimate A in place of a T, is the usual version of the gene. So CRISPR could, in theory, change DNA that would give people sickle-cell disease to DNA that would give them normal hemoglobin and hence normal blood, blood that would not cause an often life-shortening and always painful disease.

This history of overlapping inventions and scientist building on scientist—of standing on the shoulders of giants—is not unusual. It has played out unusually in this case because CRISPR is so obviously important. At stake are both fame (the Nobel Prize) and potential fortune (the patents). The history of, and credit for, CRISPR has thus become extremely controversial, often focusing on claims about the priority of the Doudna/Charpentier paper against the Zhang paper. Scores of millions of dollars have been spent on litigation over various CRISPR patents. So far, Zhang, and his employer the Broad Institute, is (more or less) winning in the U.S. while Doudna and Charpentier, and Doudna’s employer, the University of California, are heavily winning in Europe and China.

The Nobel Prize has not yet been awarded for CRISPR. Normally, this would not be a surprise for a relatively recent discovery. But CRISPR has been so universally adopted, and acclaimed, that people were predicting that some of its inventors would win the Nobel (either the prize in chemistry or the one in medicine or physiology) in 2017 or 2018. But the Nobel Committee refuses to award its scientific prizes to more than three people; some think that the prize has not yet been awarded because of the difficulties of sorting through the claims of Mojica, Doudna, Charpentier, Šikšnys, Zhang,

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44 Most commonly attributed to Isaac Newton. See Letter from Sir Isaac Newton to Robert Hooke (1675).
45 Heidi Ledford, Pivotal CRISPR patent battle won by Broad Institute, Nature News (Sep. 10, 2018), https://www.nature.com/articles/d41586-018-06656-y (accessed Feb. 27, 2019). Sarah Buhr, China sides with Emmanuelle Charpentier and Jennifer Doudna in CRISPR patent war, TechCrunch (Jun. 19, 2017), https://techcrunch.com/2017/06/19/china-sides-with-emmanuelle-charpentier-and-jennifer-doudna-in-crispr-patent-war/ (accessed Feb. 27, 2019). Kelly Servick, Broad Institute takes a hit in European CRISPR patent struggle, Science Magazine (Jan. 18, 2018), https://www.sciencemag.org/news/2018/01/broad-institute-takes-hit-european-crispr-patent-struggle/ (accessed Feb. 27, 2019).
Church, and others. Eric Lander, the director of the Broad Institute, has been widely criticized for publishing, in the high-profile journal *Cell*, a history of CRISPR (entitled ‘The Heroes of CRISPR’) that lauded Zhang’s contributions and barely mentioned Doudna.47

### B. Early Discussions of the Ethics of CRISPR’d Babies

Ethical and social concerns about CRISPR’s use, particularly in humans and especially for making babies, surfaced early. In Jan. 2015, Doudna and the U.C. Berkeley Institute for Genome Innovation, which she directed, convened a small working group for a Saturday meeting in Napa Valley. The 14 principals included some noted scientists, such as Nobel Prize winners Paul Berg and David Baltimore, and the soon-to-be-named dean of the Harvard Medical School, stem cell researcher George Daley. It also included two law professors specializing in law and biosciences: Alta Charo of the University of Wisconsin and me. The presence of Baltimore and Berg was particularly evocative; they had been two of the five scientists on the organizing committee for the Asilomar meeting on recombinant DNA, a landmark in efforts at self-regulation by science, which was held in late Feb. 1975, almost exactly 40 years earlier.48

The group’s discussions focused on the uses of CRISPR in humans, and particularly in setting where the germline would be modified. The group reached consensus surprisingly quickly. CRISPR had an important and immediate role to play with regard to *in vitro* research in humans, had great promise for use to edit the genes of people born with genetic diseases, but should not be used—at least for the time being—for germline editing. The group’s conclusions became, with the addition of a few more authors, an article published online in *Science* on Mar. 19, 2015.49 That article gave four recommendations:

Strongly discourage, even in those countries with lax jurisdictions where it might be permitted, any attempts at germline genome modification for clinical application in humans, while societal, environmental, and ethical implications of such activity are discussed among scientific and governmental organizations…

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46 Tracy Vence, ‘Heroes of CRISPR’ Disputed, *The Scientist* (Jan. 19, 2016) accessed on Mar. 6, 2019 at https://www.the-scientist.com/news-analysis/heroes-of-crispr-disputed-34188; Michael Eisen, The Villain of CRISPR, IT IS NOT JUNK (Jan. 25, 2016), http://www.michaeleisen.org/blog/?p=1825/ (accessed Mar. 12, 2019). Eisen starts his post with the arresting sentence, ‘There is something mesmerizing about an evil genius at the height of their craft, and Eric Lander is an evil genius at the height of his craft’.

47 For further discussion of the Nobel competition, the patent litigation, the history writing and their connections, see Henry T. Greely, CRISPR, Patents and Nobel Prizes: Review of A Crack in Creation, L.A. REV. BOOKS (Aug. 23, 2017).

48 Asilomar and Recombinant DNA: The End of the Beginning, BIOMEDICAL POLITICS, Kathi Hanna (ed.), Institute of Medicine (US) Committee to Study Decision Making (National Academies Press, Washington DC: 1991).

49 David Baltimore, Paul Berg, Michael Botchan, Dana Carroll, R. Alta Charo, George Church, Jacob E. Corn, George Q. Daley, Jennifer A. Doudna, Marsha Fenner, Henry T. Greely, Martin Jinek, G. Steven Martin, Edward Penhoet, Jennifer Puck, Samuel H. Sternberg, Jonathan S. Weissman, Keith R. Yamamoto, A prudent path forward for genomic engineering and germline gene modification, 348 SCIENCE 36-38 (Apr. 2015). Another article on the use of CRISPR in humans had appeared the week before in *Nature*, calling for an absolute ban on germline modifications in humans, in part to protect the valuable uses of CRISPR in gene therapy. Edward Lanphier, Fyodor Urnov, Sarah Ehlen Haecker, Michael Werner, and Joanna Smolenski, Don’t edit the human germ line,519 NATURE 410-411 (Mar. 2015).
Create forums in which experts from the scientific and bioethics communities can provide information and education about this new era of human biology, the issues accompanying the risks and rewards of using such powerful technology for a wide variety of applications including the potential to treat or cure human genetic disease, and the attendant ethical, social, and legal implications of genome modification...

Encourage and support transparent research to evaluate the efficacy and specificity of CRISPR-Cas9 genome engineering technology in human and nonhuman model systems relevant to its potential applications for germline gene therapy.

Convene a globally representative group of developers and users of genome engineering technology and experts in genetics, law, and bioethics, as well as members of the scientific community, the public, and relevant government agencies and interest groups, to further consider these important issues, and where appropriate, recommend policies.

Fairly soon, the U.S. NAS and NAM created a Human Genome Initiative. That project’s first major activity was the International Summit on Human Gene Editing, held in Washington, DC from Dec. 1 to 3, 2015, which was jointly sponsored by the NAS, the NAM, the Royal Society of the United Kingdom, and the Chinese Academy of Sciences. This highly publicized event included scores of speakers and panelists. It ended with a statement from its organizing committee (speaking for itself and not for the NAS, NAM, or other sponsors, as those entities were quick to stress). That statement’s recommendations were quite similar to those of the Mar. 2015 SCIENCE article—perhaps not surprisingly, since David Baltimore, a person not afraid to lead, chaired the organizing committee.

The short statement, which was read at the end of the three-day summit (and so necessarily prepared a little earlier) encouraged basic and clinical research as well as somatic cell clinical uses. As to germline uses, the committee concluded:

It would be irresponsible to proceed with any clinical use of germline editing unless and until (i) the relevant safety and efficacy issues have been resolved, based on appropriate understanding and balancing of risks, potential benefits, and alternatives, and (ii) there is broad societal consensus about the appropriateness of the proposed application. Moreover, any clinical use should proceed only under appropriate regulatory oversight. At present, these criteria have not been met for any proposed clinical use: the safety issues have not yet been adequately explored; the cases of most compelling benefit are limited; and many nations have legislative or regulatory bans on germline modification. However, as scientific knowledge advances and societal views evolve, the clinical use of germline editing should be revisited on a regular basis.

It ended by pointing out the international importance of the question.

While each nation ultimately has the authority to regulate activities under its jurisdiction, the human genome is shared among all nations. The international community should strive to establish norms concerning acceptable uses of human germline editing and to harmonize regulations, in order to discourage unacceptable activities while advancing human health and welfare.

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50 National Academies of Sciences, Engineering, and Medicine (NASEM), Human Genome Initiative, http://nationalacademies.org/gene-editing/index.htm/ (accessed Jan. 16, 2019).
Box 1. CRITERIA FROM THE NAS/NAM VALENTINE’S DAY REPORT

1. absence of reasonable alternatives;
2. restriction to preventing a serious disease or condition;
3. restriction to editing genes that have been convincingly demonstrated to cause or to strongly predispose to the disease or condition;
4. restriction to converting such genes to versions that are prevalent in the population and are known to be associated with ordinary health with little or no evidence of adverse effects;
5. availability of credible pre-clinical and/or clinical data on risks and potential health benefits of the procedures;
6. ongoing, rigorous oversight during clinical trials of the effects of the procedure on the health and safety of the research participants;
7. comprehensive plans for long-term, multigenerational follow-up while still respecting personal autonomy;
8. maximum transparency consistent with patient privacy;
9. continued reassessment of both health and societal benefits and risks, with broad on-going participation and input by the public; and
10. reliable oversight mechanisms to prevent extension to uses other than preventing a serious disease or condition.

And it called for an ongoing international forum to continue discussing these issues, with ‘wide range of perspectives and expertise—including from biomedical scientists, social scientists, ethicists, health care providers, patients and their families, people with disabilities, policymakers, regulators, research funders, faith leaders, public interest advocates, industry representatives, and members of the general public’.

The NAS and NAM followed up the Summit with a Feb. 14, 2017 consensus report, written by a committee of 22 after many public and private meetings. The report contains the ‘official position’ of the Academies. The Valentine’s Day report had chapters on basic research, somatic genome editing, heritable (germline) genome editing, enhancement, and public engagement. It offered clear, and strong, conclusions on germline genome editing: ‘In particular, clinical trials using heritable germline editing should be permitted only if done within a regulatory framework that includes the following [10] criteria and structures….’ These criteria, shown in Box 1, deal at some length with the condition to be addressed by the editing and the mechanisms by which it should be considered and carried out.

51 Human Genome Editing: Science, Ethics, and Governance, National Academies Press (Feb. 14, 2017), https://www.ncbi.nlm.nih.gov/books/NBK447260/ (accessed Mar. 12, 2019).
Its chapter on enhancement noted the difficulties of defining ‘enhancement’:

For example, using genome editing to lower the cholesterol level of someone with abnormally high cholesterol might be considered prevention of heart disease, but using it to lower cholesterol that is in the desirable range is less easily characterized, and would either intervention differ from the current use of statins?

That chapter concluded, ‘genome editing for purposes other than treatment or prevention of disease and disability should not proceed at this time, and that it is essential for these public discussions to precede any decisions about whether, or how, to pursue clinical trials of such applications’.

The authors pushed strongly for public engagement in decisions about genome editing, specifically recommending that, ‘With respect to heritable germline editing, broad participation and input by the public and ongoing reassessment of both health and societal benefits and risks are particularly critical conditions for approval of clinical trials’.

Some commentaries on the NAS/NAM report saw it as opposing heritable genome editing; others saw it as permissive.\(^52\) Meanwhile, in the United Kingdom, the Nuffield Council, an independent non-profit bioethics advisory group, issued two relevant reports. In 2016, it issued a general report entitled ‘Genome Editing: An Ethical Review’.\(^53\) And then, in July 2018, it issued ‘Genome Editing and Human Reproduction’, saying ‘We conclude that the potential use of heritable genome editing interventions to influence the characteristics of future generations could be ethically acceptable in some circumstances…’ Their eight requirements and recommendations, reproduced in Box 2, overlap some with those of the Valentine’s Day report but interestingly include more explicit discussion of social issues and of specific regulatory recommendations (albeit for the United Kingdom only).

The next major event in the ethical assessment of human germline genome editing was part of the efforts to have a global conversation about the topic. The Second International Summit on Human Genome Editing was scheduled to take place in Hong Kong from Nov. 27 through 29, 2018, with an (albeit non-exclusive) emphasis on speakers from Asian countries. The NAS, the NAM, and the Royal Society of the U.K. once again were three of the sponsors. For this event, however, the initial fourth sponsor, The Chinese Academy of Sciences, pulled out, for unclear

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52 Barry Coller, *Ethics of Human Genome Editing*, 70 ANNUAL REV. MEDICINE 289-305 (Jan. 2019). Jon Cohen, *Draw clearer lines around human gene editing, say leaders of Chinese and U.S. science academies*, SCIENCE MAGAZINE (Dec. 13, 2018), https://www.sciencemag.org/news/2018/12/draw-clearer-red-lines-around-human-gene-editing-say-leaders-chinese-and-us-science/ (accessed Feb. 27, 2019).

53 Nuffield Council on Bioethics (Jul 17, 2018), http://nuffieldbioethics.org/report/genome-editing-human-reproduction-social-ethical-issues/overview/ (accessed Mar. 3, 2019). Another major national report was released in May 2019 by the German Ethics Council: Deutscher Ethikrat, *INTERVENING IN THE HUMAN GERMLINE: OPINION: EXECUTIVE SUMMARY AND RECOMMENDATIONS* (May 9, 2019) (translated by Aileen Sharp), https://www.ethikrat.org/fileadmin/Publikationen/Stellungnahmen/englisch/opinion-intervening-in-the-human-germline-summary.pdf (accessed May 19, 2019). This has a thorough and excellent analysis, but as it came after the He experiment, I will not discuss it in this article.
Box 2. NUFFIELD COUNCIL REQUIREMENTS AND RECOMMENDATIONS

- it is intended to secure, and is consistent with, the welfare of a person who may be born as a consequence of interventions using genome edited cells; and
- it is consistent with social justice and solidarity, i.e. it should not be expected to increase disadvantage, discrimination, or division in society.
- We recommend that research should be carried out on the safety and feasibility of heritable genome editing interventions to establish standards for clinical use.
- We recommend that social research should be carried out to develop greater understanding of the implications of genome editing for the welfare of the future person.
- We recommend that before any move is made to amend UK legislation to permit heritable genome editing interventions, there should be sufficient opportunity for broad and inclusive societal debate.
- We recommend the establishment of an independent UK body to promote public debate on the use of genomic and related technologies to respond to societal challenges; to help to identify and understand the public interests at stake; and to monitor social, cultural, legal, and health impacts.
- We recommend that governments in the UK and elsewhere should work with international human rights institutions, such as the Council of Europe and UNESCO, to promote international dialogue and to develop a framework for international governance of heritable genome editing interventions.
- We recommend that heritable genome editing interventions should only be licensed on a case-by-case basis subject to: assessment of the risks of adverse clinical outcomes for the future person by a national competent authority (in the UK, the HFEA); and strict regulation and oversight, including long-term monitoring of the effects on individuals and social impacts.

reasons, about a year before the event and was replaced by the Academy of Sciences of Hong Kong.

C. The Law of CRISPR’ed Babies
I have quoted the recommendations from the National Academies report and the Nuffield report at length because they are the most serious and searching assessments

Sharon Begley, As a genome editing summit opens in Hong Kong, questions abound over China, and why it quietly bowed out, STAT (Nov. 26, 2018), https://www.statnews.com/2018/11/26/human-genome-editing-summit-china/ (accessed Feb. 27, 2019).
that I know of on human germline genome editing. Between them, they contain 18 thoughtful, careful guidelines. Neither report, however, has the force of law—in the U.S., in the U.K., or anywhere else. So: what does the law say?

In the U.K., the answer is clear. The Human Fertilisation and Embryology Act of 1990 specifically ban any uses of genome editing techniques in human embryos, eggs, or sperm intended for use in reproduction. In vitro research use that does not involve the transfer of an embryo to a uterus for possible implantation, development, and birth is legal, if licensed by the Human Fertilisation and Embryology Authority. 55

Although the definitions and details vary, many other countries join the U.K. in having bans on germline modification in human reproduction. A 2016 publication counts at least 11 countries with express bans on the procedure, including Canada, Brazil, the United Kingdom, France, the Netherlands, Belgium, Germany, India, South Korea, Japan, and Australia. 56

The situation is the United States is more complicated, but its law also, ultimately, bans human germline genome editing in reproduction. Since its reaction to the possibility of human reproductive cloning nearly twenty years ago, the U.S. Food and Drug Administration (FDA) has taken the position that any genetically, or otherwise substantially-modified, human embryo is a drug or biological product, the clinical use of which requires FDA approval. Full clinical use would require a sponsor to receive a New Drug Approval (NDA) (if it is viewed as a drug) or a Biological License Approval (BLA) (if a biological product). Each would require lengthy, expensive, and painstaking proof that the process was safe and effective. 57

A sponsor for a drug or biological product must conduct clinical trials in humans in order to gather the information to get an NDA or a BLA, and the sponsor must receive an Investigational New Drug Exemption (IND) from the FDA in order to administer the drug or biological product even in research. To receive an IND, the sponsor must file with FDA some evidence that, based on trials in non-human animals or in human cells in vitro (or both), the drug or biologic is both apparently safe and somewhat promising. FDA does not have to ‘approve’ the IND application; the filing sponsor automatically gets an IND 30 days after filing unless FDA blocks the IND, as it sometimes does.

There is no reason to think that FDA, based on the current (grossly lacking) information on safety and efficacy of CRISPR in human embryos, would allow an IND to go into effect, let alone approve an NDA or a BLA. This is true on strict scientific grounds, as a gateway matter, without even considering the possible influence of political opposition to such efforts, opposition that could affect decisions by FDA or by the Secretary of Health and Human Services, to which FDA reports. 58 Moving a modified embryo into a human uterus would then be considered the distribution of an unapproved drug

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55 Human Fertilisation and Embryology Act, 1990, ch. 37 (Eng.) § 3.
56 Rosario Isasi, Erika Kleiderman and Bartha Maria Knoppers, Editing Policy To Fit the Genome?, 351 SCIENCE 6271, 73 (2016).
57 United States Food and Drug Administration, Refuse to File: NDA and BLA Submissions to CDER, Guidance for Industry (Dec. 2007).
58 In 2011, HHS overruled FDA for the first time ever. HHS Secretary Kathleen Sebelius disallowed emergency contraceptives from being sold over the counter to teenagers 16 or younger, even though FDA Commissioner Margaret Hamburg had issued a statement saying that it would be safe to allow this. Gardiner Harris, Plan to Widen Availability of Morning-After Pill Is Rejected, THE N.Y. TIMES (Dec. 7, 2011),
or biological product, which is a violation of the FDA’s authorizing statutes and can be punished with civil and criminal penalties.

Even though FDA almost certainly would not, any time soon, allow even an IND for germline editing to go into effect, Congress took preemptive action of its own to bind FDA’s hands. In Dec. 2015, an amendment was added to the legislation appropriating funds to FDA. In relevant part, it said:

none of the funds made available by this Act may be used to notify a sponsor or otherwise acknowledge receipt of a submission for an exemption for investigational use of a drug or biological product under section 505(i) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(i)) or section 351(a)(3) of the Public Health Service Act (42 U.S.C. 262(a)(3)) in research in which a human embryo is intentionally created or modified to include a heritable genetic modification. Any such submission shall be deemed to have not been received by the Secretary, and the exemption may not go into effect.59

Although acts appropriating funds are generally only binding for one year of appropriations, the rider, in the same language, has been renewed every year and remains in effect today.60

So, to summarize: genome editing for human reproduction is only legal in the U.S. with FDA approval, either for research or for clinical use, but FDA is forbidden to consider or allow such use—and no application to FDA for an IND will even be considered ‘received’, presumably no matter how many witnesses can swear that it was handed to an FDA official.

D. He Jiankui

We do not know much about He Jiankui61 but we do know a few things. He is generally accepted to be a smart and ambitious young scientist. Early biographical details on He are limited; he says he was born to a farming family in Hunan province in 1984. He received his undergraduate degree in 2006 at the University of Science and Technology of China, a highly regarded Chinese university in Hefei, Anhui Province. He then entered a graduate program at Rice University in Houston, Texas, receiving his Ph.D. in biophysics in 2010 (apparently in four years) under the supervision of Professor Michael Deem. During the calendar year of 2011 he was a post-doctoral scholar in the laboratory of Professor Steven Quake at Stanford University, where he studied single cell analysis. He was lured back to China in 2012 as part of the government’s Thousand Talents program and was appointed to the faculty of the Southern University of Science and Technology, in Shenzhen, in Guangdong Province.

Jing-Bao Nie, a professor at the Bioethics Centre at the University of Otago in New Zealand, put He’s career trajectory in China in perspective in the following lengthy excerpt from her article in the HASTINGS CENTER BIOETHICS FORUM:

https://www.nytimes.com/2011/12/08/health/policy/sebelius-overrules-fda-on-freer-sale-of-emergency-contraceptives.html/ (accessed Feb. 27, 2019).

59 Consolidated Appropriations Act, 2016, § 749.
60 A similar appropriations rider, banning federal funding for any research that destroyed or threatened harm to any human embryo that was not directly aimed at treating that particular embryo, the so-called Dickey-Wicker Amendment, has been renewed every year since 1995.
61 His name is very difficult for most non-Chinese speakers to pronounce and when studying in the United States, he asked people to call him ‘JK’, which they gratefully did.
Although currently under investigation by Chinese authorities, He Jiankui has become a rising science star in China. Since his youth, he has been known to people around him as an aspiring Chinese Einstein. He first studied physics in China. In the United States, he shifted to genetics, particularly gene-editing technologies, for its greater potential to realize his ambition. He returned to China because he believed he would be able to ‘gan dashi’ (accomplish something tremendous) there and only there.

He Jiankui has been a darling of China’s current system of sciences. He has many accolades and received extremely generous support from central and local governments and scientific organizations. He was recruited to the Southern University of Science and Technology in Shenzhen through the city’s ‘Talent Peacock Plan’ in 2012. His research has been funded by grants from the government of Guangdong Province and the Ministry of Science and Technology. In 2018, he was nominated for the China Youth Science and Technology Award of the Central Government and the Chinese Association of Science and Technology. More importantly, He was selected to the Central Government’s top science program, Qianren Jihua (Thousand Talents Plan). The plan claims to be ‘world’s most prestigious and influential state science program’, involving almost every department of the government. The program’s overall goal is to advance a number of specific scientific and financial areas, such as gene technologies and genetics industry, that the state deems to be of primary strategic importance.

Taking advantage of the enormous official efforts to commercialize scientific research, He Jiankui has also been a rising entrepreneurial star in China in just five or six years. With governmental, domestic and international investment, He has become the owner and/or significant shareholder of at least seven gene companies, being worth of at least a few billion yuan (more than half a billion U.S. dollars). One of them is Direct Genomics Biotechnology, which He chairs. But, in their paper on the ethics of germline gene-editing published online in The CRISPR Journal on Nov. 28, He and his team declared ‘no competing financial interests’. Nor were any funding sources of their research disclosed.62

He’s doctorate is in biophysics. Although he and his advisor, Rice professor Michael Deem, published one paper in 2010 on CRISPR, according to its abstract it had little to do with editing embryos’ genes.

We propose a population dynamics model that explains the biological observation that the leader-proximal end of CRISPR is more diversified and the leader-distal end of CRISPR is more conserved...Our results show that the CRISPR spacer structure is influenced by and provides a record of the viral challenges that bacteria face’.63

This finding has no apparent connection to the use of CRISPR as a biotech tool (an idea that was not published for another two years) but rather involved the natural history of CRISPR in bacteria. As far as I can tell, it was not a major contribution to the CRISPR literature. He’s one-year post-doc with Dr. Quake had no connection to CRISPR. When he returned to China, He founded a biotech company called Direct

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62 Jing-Bao Nie, He Jiankui’s Genetic Misadventure: Why Him? Why China?, HASTINGS CENTER BIOETHICS FORUM (Dec. 5, 2018), https://www.thehastingscenter.org/jiankui-genetic-misadventure-china/ (accessed Jan. 20, 2019).
63 He Jiankui and Michael Deem, Heterogeneous diversity of spacers within CRISPR (clustered regularly interspaced short palindromic repeats), 105 PHYS. REV. LETT. 128102 (2010).
Genomics based on Quake’s work and patents, but it sought to develop DNA sequencing devices that would work on single molecules, something not particularly connected to CRISPR or to human germline genome editing.

It is not clear when or how He became interested in editing human embryos. Nothing in his past work seems relevant to that task. He is not a physician, let alone a reproductive endocrinologist or an obstetrician/gynecologist, the clinical specialties with expertise in assisted reproduction. He had no expertise in using CRISPR in embryos, human or non-human, and absolutely no expertise in assisted reproduction. He’s work with Quake might have given him some advantages in determining the whole genome sequences from a sample of only one or two cells from an embryo, but that is a minor aspect of the experiments he reported.

Somehow, sometime, and for some reason—pursuit of fame seems plausible, for this rising star in the Chinese scientific community—He did become interested in embryo editing. He was invited to present his work at Cold Spring Harbor Laboratories in July 2017, on the topic of ‘Evaluating the safety of germline genome editing in human, monkey and mouse embryos’. In his presentation, which is available on YouTube, he discussed the results of his work in using CRISPR to modify embryos in mice, monkeys, and over 300 human embryos. If true, he must have been working on CRISPR in embryos for months, or even years, before 2017. Although, note that, much like his alleged CRISPR’d twin girls, this work has not been published or otherwise independently verified.

IV. THE REVELATION OF THE HE EXPERIMENT AND ITS FALLOUT

The way knowledge of He’s experiment unfolded seems like something out of a novel—but a real-life novel which we can still trace through Twitter, YouTube, and online posts. It is not clear to me how important the course of the revelation is, but I find it fascinating and my description of it follows, in seven parts: before the Summit, outside Hong Kong; before the Summit, in Hong Kong; at the Summit; after the Summit; before the Summit, but not disclosed until afterwards; Michael Deem’s role; and other information that exists but has not yet been revealed.

A. Before the Start of the Summit—Outside Hong Kong

Antonio Regalado was the first to suggest that He had conducted unprecedented experiments. Regalado tweeted about an article he had just posted to MIT TECHNOLOGY REVIEW at 7:15 p.m. EST, Sunday, Nov. 25, which was mid-morning on Monday, Nov. 26 in Hong Kong. The article, initially entitled ‘EXCLUSIVE: Chinese Scientists Planning to Make CRISPR Babies’, reported:

According to Chinese medical documents posted online this month … a team at the Southern University of Science and Technology, in Shenzhen, has been recruiting couples in an effort to create the first gene-edited babies. They planned to eliminate a gene called CCR5 in hopes of rendering the offspring resistant to HIV, smallpox, and cholera.

64 Jiankui He talking about human genome editing, YouTube (Jul 29, 2017), https://www.youtube.com/watch?v=llxNRGMxyCc (accessed Mar. 12, 2019).
65 Later retitled to: ‘EXCLUSIVE: Chinese scientists are creating CRISPR babies’.
66 Regalado, supra note 4.
Regalado, who, not for the first time, demonstrated impressive skills as an investigative reporter, had discovered this by examining the WHO’s ChiCTR, the equivalent for China of clinicaltrials.gov, the National Institutes of Health website in the U.S. that includes a list of all experimental trials in humans (whose sponsors submit them for listing). Regalado continued:

The clinical trial documents describe a study in which CRISPR is employed to modify human embryos before they are transferred into women’s uteruses.

The scientist behind the effort, He Jiankui, did not reply to a list of questions about whether the undertaking had produced a live birth. Reached by telephone, he declined to comment.

However, data submitted as part of the trial listing shows that genetic tests have been carried out on fetuses as late as 24 weeks, or six months. It’s not known if those pregnancies were terminated, carried to term, or are ongoing.

Within two and a half hours, Regalado’s question had been, at least apparently, answered. At 6:42 p.m. PST, Eric Topol, a physician-researcher, tweeted about an ASSOCIATED PRESS (AP) story by Marilyn Marchione, entitled ‘Chinese Researcher Claims First Gene-Edited Baby’. 67

Marchione’s story totaled over 1700 words—so she clearly did not write it in the 150 minutes that had elapsed since Regalado’s piece appeared. (The story was dated November 26, but 6:00 pm, Nov. 25 on the U.S. West Coast was 10:00 a.m. Monday, Nov. 26 in Hong Kong.) Marchione listed three contributors in China to the article’s research and said it was part of an ‘Associated Press series produced in partnership with the Howard Hughes Medical Institute’s Department of Science Education’. It turned out that AP had been talking with He for over a month before the story broke, and they were forced into the open by Regalado’s scoop. Surprisingly, and perhaps disingenuously, the AP story never mentioned Regalado’s piece.

What did the AP story say? Marchione led with this: ‘A Chinese researcher claims that he helped make the world’s first genetically edited babies—twin girls born earlier this month whose DNA he said he altered ….’ 68 The researcher said he altered embryos for seven couples during fertility treatments, with one pregnancy resulting so far. He stated that his goal was not to cure or prevent an individual disease, but to try to bestow a trait that few people naturally have—an ability to resist possible future infection with HIV, the AIDS virus.

Marchione stated that: ‘He said he practiced editing mice, monkey, and human embryos in the lab for several years and has applied for patents on his methods. He said he chose embryo editing for HIV because these infections are a problem in China. He sought to disable a gene called CCR5 that forms a protein doorway that allows HIV, the virus that causes AIDS, to enter a cell.’

The prospective parents were couples where the man was HIV-infected, while the woman was not. These couples were recruited through an AIDS advocacy group named

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67 Marchione, supra note 5.
68 Id.
Baihualin and were inspired by idea that their children would be immune to the disease. They also received free fertility treatments, medical care for the pregnancy, and a stipend. The total value of the benefits for those whose babies were born has been stated, based on the Chinese consent form, as the equivalent of about $40,000.\footnote{Krimsky, supra note 19.}

Marchione says he described his work as follows:

The gene editing occurred during IVF, or lab dish fertilization. First, sperm was ‘washed’ to separate it from semen, the fluid where HIV can lurk. A single sperm was placed into a single egg to create an embryo. Then the gene editing tool was added.

When the embryos were 3 to 5 days old, a few cells were removed and checked for editing. Couples could choose whether to use edited or unedited embryos for pregnancy attempts. In all, 16 of 22 embryos were edited, and 11 embryos were used in six implant attempts before the twin pregnancy was achieved, He said.

Tests suggest that one twin had both copies of the intended gene altered and the other twin had just one altered, with no evidence of harm to other genes, He said. People with one copy of the gene can still get HIV, although some very limited research suggests their health might decline more slowly once they do.\footnote{Marchione, supra note 5.}

Dr. He claimed he had ethics approval from Shenzhen Harmonicare Women’s and Children’s hospital, but he did not claim approval from his home institution or the four (unnamed) hospitals that provided the embryos. The article quotes Dr. Liu Zhitong, the head of Harmonicare’s ethics panel, as saying ‘we think this is ethical’.

The article also discusses Michael Deem, He’s Ph.D. advisor from Rice University:

The U.S. scientist who worked with him on this project after He returned to China was physics and bioengineering professor Michael Deem, who was his adviser at Rice in Houston. Deem also holds what he called ‘a small stake’ in — and is on the scientific advisory boards of — He’s two companies.

Marchione adds:

The Rice scientist, Deem, said he was present in China when potential participants gave their consent and that he ‘absolutely’ thinks they were able to understand the risks.

Deem told AP that he worked with He on vaccine research at Rice and considers the gene editing similar to a vaccine. ‘That might be a layman’s way of describing it’, he said.

Regalado and Marchione’s pieces were just the start. Much more came out that (US) Sunday night. At some point on Nov. 25—I cannot determine when, or in what time zone—the He lab posted five short videos on YouTube, four of them featuring He, who spoke (in English) about the gene-edited babies.\footnote{About Lulu and Nana: Twin Girls Born Healthy After Gene Surgery As Single-Cell Embryos, https://www.youtube.com/watch?v=th0vnOmFltc/ (accessed Jan. 19, 2019); ‘Designer Baby’ Is an Epithet, https://www.youtube.com/watch?v=Qy1swMfaTWU/ (accessed Jan. 19, 2019); Why}
by Dr. Qin Jinzhou, the lab’s embryologist, speaking in Chinese (with subtitles in Chinese and English), about the twins. Like the AP article, these videos had clearly had been produced well in advance of Regalado’s revelation. Interestingly, the AP story did not mention these videos, saying that He had revealed his work only ‘Monday in Hong Kong to one of the organizers of [the Summit] that is set to begin on Tuesday, and earlier in exclusive interviews with The Associated Press’.

One more piece needs to be added. Sometime on Monday, Nov. 26, THE CRISPR JOURNAL, a relatively new journal from Mary Ann Liebert, Inc., published an article, with He as lead author, entitled ‘Draft Ethical Principles for Therapeutic Assisted Reproductive Technologies’. The JOURNAL has told me that the He paper was received on Nov. 5. They sent it out for expedited peer review in the hope of publishing it before the Hong Kong summit, but knew nothing of He’s efforts to make babies until the story broke in the press. On Nov. 18, the JOURNAL accepted it in principle, subject to some revisions. They received the revisions the next day and accepted the manuscript, scheduling it for publication on Monday, Nov. 26, EST (the time zone of their editorial office). On the day after publication (and after revelation of the experiment), the editor-in-chief, Rodolphe Barrangou, and the executive editor, Kevin Davies, wrote to He, requesting a revised Conflict of Interest form. The original form declared no conflicts. The article was eventually retracted towards the end of Feb. 2019 on the grounds that the authors had failed to properly disclose certain conflicts.

In the article, He and his co-authors said:

[W]e have thought deeply about ethical foundations for regulation in discussions between researchers, patients and advocates, and ethicists both in China and abroad. These discussions lead us to propose that, at a minimum, five core principles should be addressed in a modernization of Chinese regulations—and indeed any country’s guidelines or laws—permitting gene surgery for ART: (1) a clear social purpose, (2) impermissible uses, (3) rights after treatment, (4) the human spirit’s transcendence of DNA, and (5) a special duty to reduce economic inequality.

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We Chose HIV and CCR5 First, https://www.youtube.com/watch?v=aezzaOn0efE/ (accessed Jan. 19, 2019); and Draft Ethical Principles of Therapeutic Assisted Reproductive Technologies, https://www.youtube.com/watch?v=MyNHpMoPkg/ (accessed Jan. 19, 2019).

72 Gene Surgery in Embryos, supra note 25.

73 He Jiankui, Ryan Ferrell, Chen Yuanlin, Qin Jinzhou, Chen Yangran, Draft Ethical Principles for Therapeutic Assisted Reproductive Technologies, 1 The CRISPR J. 6 http://doi.org/10.1089/crispr.2018.0051/. The five authors are shown as affiliated with He’s institution, the Southern University of Science and Technology in Shenzhen; Qin, the embryologist, also has an appointment with the Department of Reproductive Medicine Center, Third Affiliated Hospital of Shenzhen University. The second author, Ryan Ferrell is said to be an American public relations consultant, Ed Yong, The CRISPR Baby Scandal Gets Worse by the Day, The Atl, https://www.theatlantic.com/science/archive/2018/12/15-worrying-things-about-crispr-babies-scandal/577234/ (accessed Jan. 19, 2019) and He’s spokesman, David Cyranoski, First CRISPR Babies: Six Questions That Remain, Nature (Nov. 30, 2018), https://www.nature.com/articles/d41586-018-07607-3 (accessed Jan. 19, 2019).

74 Email communication from Kevin Davies to Henry T. Greely (Jan. 21, 2019).

75 Julianna LeMieux, He Jiankui’s Germline Editing Ethics Article Retracted by The CRISPR Journal, GEN (Feb. 20, 2019), https://www.genengnews.com/featured/he-jiankuis-germline-editing-ethics-article-retracted-by-the-crispr-journal/ (accessed Feb. 26, 2019).

76 Jiankui et al., supra note 73.
A box in the paper explains these five ‘core principles’ though using different terminology.

1. Mercy for families in need…

A broken gene, infertility, or a preventable disease should not extinguish life or undermine a loving couple’s union. For a few families, early gene surgery may be the only viable way to heal a heritable disease and save a child from a lifetime of suffering.

2. Only for serious disease, never vanity …

Gene surgery is a serious medical procedure that should never be used for aesthetics, enhancement, or sex selection purposes—or in any way that would compromise a child’s welfare, joy, or free will. No one has a right to determine a child’s genetics except to prevent disease. Gene surgery exposes a child to potential safety risks that can be permanent. Performing gene surgery is only permissible when the risks of the procedure are outweighed by a serious medical need.

3. Respect a child’s autonomy …

A life is more than our physical body and its DNA. After gene surgery, a child has equal rights to live life freely, to choose his or her occupation, to citizenship, and to privacy. No obligations exist to his or her parents or any organization, including paying for the procedure.

4. Genes do not define you …

Our DNA does not predetermine our purpose or what we could achieve. We flourish from our own hard work, nutrition, and support from society and our loved ones. Whatever our genes may be, we are equal in dignity and potential.

5. Everyone deserves freedom from genetic disease…

Wealth should not determine health. Organizations developing genetic cures have a deep moral obligation to serve families of every background.

Why this long discussion of how He’s work came to be known? In part because it seems interesting, but in part to wonder, when was He planning to reveal the twins? I have found no discussion of that. Clearly, between the AP story and the five YouTube videos, he was ready to do so at the proverbial moment’s notice. Given that he had speaking slots at the Hong Kong summit, it is hard to not to conclude that he intended to announce the babies from its stage.

77 Chinese characters contained in the original and presumably meaning the same as the English words are omitted.
B. Just Before the Summit—in Hong Kong

My conclusion is reinforced by a recent statement by Jennifer Doudna, one of the inventors of CRISPR and a member of the Summit’s organizing committee. Doudna said she first got word of He’s work in an email from him, which she received on Thanksgiving Day, Nov. 22, three days before the Regalado piece. The email had the subject line ‘Babies Born’. Doudna was quoted saying, ‘I was just horrified; I felt kind of physically sick’. It is not clear to whom Doudna passed on this information, but she says she changed her travel plans and left a day earlier for Hong Kong.

Doudna seems to have been the first member of the organizing committee to learn about He’s babies. In fact, Robin Lovell-Badge, who moderated the panel He presented on, said from the podium at the Summit that he had reviewed He’s submitted slides, which included only preclinical work and did not refer to the babies. One might ask about the fairness of that to the conference organizers. (Of course, one might also ask whether, once they learned of He’s work, the conference organizers should have allowed such ethically questionable research to be presented at the Summit).

Given that He told Doudna, one of the Summit organizers, on the Thursday before the Tuesday opening of the Summit, on whose organizing committee he served, it seems likely he intended to announce his experiment at the summit. On the other hand, Doudna told STAT that, when she met He in the lobby of the conference hotel sometime on Monday, he told her that he didn’t intend to talk about the babies at all.

Um, Doudna replied, you’ve dropped this shocking news on the world, right before our summit, and you’re not planning to mention it? He seemed surprised that she expected him to but agreed to have dinner with her and other members of the summit organizing committee that evening to talk it out.

On balance, I’m inclined to agree with Kiran Musunuru, a scientist at the University of Pennsylvania, when he said ‘I suspect he was planning to pull a Steve Jobs style ‘One last thing’ during his talk’. What more dramatic reveal could he hope for?

Pam Belluck, How to Stop Rogue Gene Editing of Human Embryos?, THE N.Y. TIMES (Jan. 23, 2019) https://www.nytimes.com/2019/01/23/health/gene-editing-babies-crispr.html/. (accessed Jan. 19, 2019).

Id.

A traveler from California to Hong Kong arrives, even on a non-stop flight, about 31 hours later than departing because of the date change at the International Dateline; thus if Doudna left San Francisco on a Friday midday departure, she would arrive at the Hong Kong airport on Saturday night.

Session 3 – Human Embryo Editing, Second International Summit on Human Genome Editing, http://www.nationalacademies.org/gene-editing/2nd-summit/second-day/index.htm (accessed Feb. 28, 2019). On May 21, the Academies released a summary of the Second International Summit: National Academies of Sciences, Engineering, and Medicine, Second International Summit on Human Genome Editing: Continuing the Global Discussion: Proceedings of a Workshop in Brief (2019, Washington, DC: The National Academies Press. https://doi.org/10.17226/25343, https://www.nap.edu/catalog/25343/second-international-summit-on-human-genome-editing-continuing-the-global-discussion (accessed May 21, 2019). (Note: I was one of the reviewers on this short report.)

Sharon Begley and Andrew Joseph, The CRISPR shocker: How genome-editing scientist He Jiankui rose from obscurity to stun the world, STAT (Dec. 17, 2018), https://www.statnews.com/2018/12/17/crispr-shocker-genome-editing-scientist-he-jiankui/ (accessed Feb. 28, 2019).

Antonio Regalado, Years before CRISPR Babies this Man was the First to Edit Human Embryos, MIT TECH. REV. (Dec. 11, 2018), https://www.technologyreview.com/s/612554/years-before-crispr-babies-this-man-was-the-first-to-edit-human-embryos/ (accessed Mar. 12, 2019).

This would mean that He had misled Doudna in the hotel lobby; that seems to me quite plausible.
Members of the organizing committee who were already in Hong Kong—or who landed there during Monday—had to scramble quickly to decide what to do. Doudna and three other members of the organizing committee met for dinner with He on Monday night, Nov. 26, to discuss his work. *Science* reported:

On the eve of the International Summit on Human Genome Editing in Hong Kong, China, last week, He, a researcher at nearby Southern University of Science and Technology in Shenzhen, China, had dinner at the city’s Le Méridien Cyberport with a few of the meeting’s organizers. The news of He’s claim had just broken, and shock waves were starting to reverberate. But the reports were still so fresh that the diners sat in the restaurant without being disturbed.

‘He arrived almost defiant’, says Jennifer Doudna, who did landmark CRISPR work at the University of California (UC), Berkeley. She and the other conference organizers politely asked He questions about the scientific details and rationale of his work, the permissions he had secured to conduct it, and how he recruited hopeful parents to participate and informed them about risks. He asked them whether his planned talk two days later should include data about the twin girls, who had a gene altered to make them resistant to HIV infection. We were all like, ‘Uh, yes’, Doudna says.

After more than an hour of questioning, He had had enough. ‘He just seemed surprised that people were reacting negatively about this’, Doudna says. ‘By the end of the dinner he was pretty upset and left quite abruptly’.  

The organizing committee decided that He would give his scheduled talk on the second day of the summit, Wednesday, Nov. 28, as part of a panel called ‘Human Embryo Editing’, moderated by Robin Lovell-Badge and including presentations from Kathy Niakan, Paula Amato, Maria Jasin, and Xingxu Huang. He would be the last to speak, and he was also scheduled to be on a panel on Thursday, Nov. 29, on developing standards for human genome editing.

The Organizing Committee released a statement on Monday, Nov. 26, at around 1:00 p.m. EST. That would be about 11:00 p.m. Monday in Hong Kong, presumably after the dinner and just a few hours before the meeting’s start.  

The criteria under which heritable genome-editing clinical trials could be deemed permissible have been the subject of much debate and discussion by many research groups …. Whether the clinical protocols that resulted in the births in China conformed with the guidance in these studies remains to be determined.

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85 Jon Cohen, After Last Week’s Shock, Scientists Scramble to Prevent More Gene-Edited Babies, Science (Dec. 4, 2018).

86 The earliest tweet on the statement is timestamped 12:56 p.m. on Nov. 26. The poster works in Washington, D.C., which leads me to conclude that the posting time shown is EST. See https://twitter.com/greg_folkers/status/1067114895651557376.
We hope that the dialogue at our summit further advances the world’s understanding of the issues surrounding human genome editing. Our goal is to help ensure that human genome editing research be pursued responsibly, for the benefit of all society.

C. At the Summit
The Summit opened on Tuesday morning with the usual welcomes and charges from local dignitaries and organizers. Four panels—two on science, one on ethics, and one on law—followed that day until the meeting’s 6:00 p.m. adjournment. No one focused on the He experiment.

The ‘Human Embryo Editing’ panel was the third session on the following day, Wednesday. This panel was live streamed, in China and around the world. British scientist Robin Lovell-Badge, a member of the organizing committee, moderated the panel. Drs. Niakan, Amato, Jasin, and Huang gave their presentations and took questions for the first hour and fifteen minutes of the panel, which had been allocated a total of 90 minutes. At that point, these four speakers left the stage, and the moderator, Robin Lovell-Badge, implored the audience not to interrupt He—telling the audience that he, Lovell-Badge, had the right to cancel the session if there were too many interruptions, and reminding everyone of the Hong Kong University’s long tradition of free speech.

Dr. He presented his results for about 20 minutes, starting with mouse work and then moving to the babies. Afterwards, He was questioned on stage by Lovell-Badge and Dr. Matthew Porteus, another scientist-member of the Organizing Committee, for about 15 minutes. David Baltimore, the chair of the organizing committee got up to speak, reinforcing the need for societal consensus, arguing that further research would be irresponsible, and decrying that the experiment was neither transparent nor medically-necessary. Baltimore called this ‘a failure of self-regulation by the scientific community, because of a lack of transparency’. 87 For the remaining 25 minutes, He spoke with the moderators and then took questions from the audience.

Lovell-Badge questioned the selection of \textit{CCR5} given how little we know about it—particularly given some research that indicated it could make the babies more susceptible to influenza, and other research suggesting that editing \textit{CCR5} could enhance cognitive abilities. Dr. He responded that the gene had been ‘studied for decades’, and that he was against using editing for enhancement. Porteus asked how many women were part of He’s ‘pipeline’ for his experiment, which is how we know (or think we know) that eight women were selected and one dropped out. Dr. He explained that 31 embryos were injected, of which 70 % were edited. He also explained that the clinical trial had ended given the ‘current situation’.

Porteus wanted to know how the trial and the consent process were designed. Dr. He referred to his Cold Spring presentation, where he apparently got feedback and criticism from some attendees; he also spoke with ‘top ethicists in the United States’, and had ‘a US professor’ and ‘a Chinese professor’ review his consent, along with the four people on his team. According to He, he personally spent one hour and ten minutes with each participant to explain the consent, after each participant had spent two hours with one of his team members. He was confident that the women were ‘very educated’ and could understand the consents.

\footnote{Session 3, supra note 81.}
At this point, the moderators opened it up to questions from the general audience and from the media. David Liu from the Broad Institute questioned whether the experiment satisfied an ‘unmet medical need’, since sperm-washing technology can prevent prenatal paternal transmission of HIV, and asked about the role of scientists in making decisions for patients. Dr. He said he felt proud about what he had done, to help the children survive, since HIV is such a horrible affliction. When pressed by another audience member on the ethics of his experiment, He said he was showing compassion by using available technology to help people with genetic disease.

Porteous interjected to ask if there were more pregnancies, and He told him that there was one. In a particularly difficult moment towards the end of the session, when Dr. Jasin from Sloan-Kettering asked about the personal impact on Nina and Lulu and the family dynamics between them, given the disparate outcomes of the experiment, He explained that he wanted to give them ‘freedom of choice’, but did not know how to answer when Dr. Jasin pressed him to consider how the families and the children, themselves, would deal personally with the fact that their genes had been edited.

At the end of the panel, He said he did not anticipate such a strong reaction from the international community.

After the audience questions, He left the stage, and, shortly thereafter, left Hong Kong to return to mainland China. He cancelled his scheduled appearance at the Thursday panel. Since then, he has made no substantive statements on the research.

D. After the Summit—Reactions

Dr. He said that he did not anticipate a strong reaction to his experiment. So how did the world react? Two sets of reactions are particularly interesting. One is from the scientific community around the world; the other is from voices in China.

1. Scientific Reactions Around the World

Even before He’s talk, the first ASSOCIATED PRESS article contained strongly worded comments on his work by three prominent scientists.

Some scientists were astounded to hear of the claim and strongly condemned it. It’s ‘unconscionable …. an experiment on human beings that is not morally or ethically defensible’, said Dr. Kiran Musunuru, a University of Pennsylvania gene editing expert and editor of a genetics journal.

‘This is far too premature’, said Dr. Eric Topol, who heads the Scripps Research Translational Institute in California. ‘We’re dealing with the operating instructions of a human being. It’s a big deal’.

However, one famed geneticist, Harvard University’s George Church, defended attempting gene editing for HIV, which he called ‘a major and growing public health threat’.

‘I think this is justifiable’, Church said of that goal.88

This set the tone for comments after the presentation—everyone expressed opposition to He’s work, except George Church.

88 Marchione, supra note 5.
At the end of the Summit, its organizing committee issued a 10-paragraph statement. It stated, 'The organizing committee concludes that the scientific understanding and technical requirements for clinical practice remain too uncertain and the risks too great to permit clinical trials of germline editing at this time'. The statement continued:

At this summit we heard an unexpected and deeply disturbing claim that human embryos had been edited and implanted, resulting in a pregnancy and the birth of twins. We recommend an independent assessment to verify this claim and to ascertain whether the claimed DNA modifications have occurred. Even if the modifications are verified, the procedure was irresponsible and failed to conform with international norms. Its flaws include an inadequate medical indication, a poorly designed study protocol, a failure to meet ethical standards for protecting the welfare of research subjects, and a lack of transparency in the development, review, and conduct of the clinical procedures.

This language was restrained compared to the assessments of some critics. Ed Yong hit some of the high points in an article in The Atlantic:

The CRISPR pioneer Jennifer Doudna says she was ‘horrified’, NIH Director Francis Collins said the experiment was ‘profoundly disturbing’, and even Julian Savulescu, an ethicist who has described gene-editing research as ‘a moral necessity’, described He’s work as ‘monstrous’.90

I was quoted (accurately) as saying ‘This is criminally reckless and I unequivocally condemn the experiment’,91 and as calling the work ‘Grossly premature and deeply unethical’.92

Almost alone on the other side was George Church. Church, an immensely creative scientist at Harvard Medical School who often takes controversial positions, defended He’s work in comments to several news sources. In an interview with Science, he said:

I’d just as well not hang myself out to dry with someone I barely know, but I feel an obligation to be balanced about it. I’m sitting in the middle and everyone else is so extreme that it makes me look like his buddy. He’s just an acquaintance. But it seems like a bullying situation to me. The most serious thing I’ve heard is that he didn’t do the paperwork right. He wouldn’t be the first person who got the paperwork wrong. It’s just that the stakes are higher. If it had gone south and someone had been damaged, maybe there would be some point. Like what happened with Jesse Gelsinger [who died in a 1999 gene therapy

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89 On Human Genome Editing II: Statement by the Organizing Committee of the Second International Summit on Human Genome Editing (Nov 29, 2018), http://www8.nationalacademies.org/onpinews/newsitem.aspx?RecordID=11282018b&ga=2.241822785.21631665.1543473766-946872498.1543313092/ (accessed Feb. 28, 2019).

90 Yong, supra note 73.

91 Christina Farr, Experiments to gene-edit babies are ‘criminally reckless’, says Stanford bio-ethicist, CNBC (Nov. 26, 2018), https://www.cnbc.com/2018/11/26/hinese-crispr-baby-gene-editing-crимinally-reckless-bio-ethicist.html (accessed Mar. 12, 2019).

92 Lauran Neergaard and Malcolm Ritter, Q&A on scientist’s bombshell claim of gene-edited babies, Associated Press (Nov. 26, 2018), https://www.apnews.com/69c325fc818d4da0902357595a602238 (accessed Mar. 12, 2019).
experiment]. But is this a Jesse Gelsinger or a Louise Brown [the first baby born through in vitro fertilization] event? That’s probably what it boils down to.93

A few weeks later, on Dec. 14, something close to an ‘official’ voice of Science weighed in, in SCIENCE magazine. Victor Dzau, the president of the U.S. National Academy of Medicine; Marcia J. McNutt, the president of the U.S. National Academy of Sciences; and Chunli Bai, president of the Chinese Academy of Sciences, published an editorial entitled ‘Wake-up Call from Hong Kong’. In it, they said:

the case highlights the urgent need to accelerate efforts to reach international agreement upon more specific criteria and standards that have to be met before human germline editing would be deemed permissible. Together, we call upon international academies to quickly convene international experts and stakeholders to produce an expedited report that will inform the development of these criteria and standards to which all genome editing in human embryos for reproductive purposes must conform, and to engage scientific bodies around the world in this effort.94

2. Chinese Reactions
It was not immediately clear how China, and the Chinese, would react. The first Chinese story on He’s work trumpeted it as a great accomplishment of Chinese science.95

That mood quickly changed. Almost immediately—on Nov. 26—a group of 122 Chinese scientists and ethicists published a joint statement on WeChat, a Chinese messaging and payments app, calling the work ‘madness’ and demanding stronger rules against such research. ‘We can only use the word ‘crazy’ to describe the experiment conducted directly on human beings’.96 Many other prominent Chinese scientists condemned the experiment the same day and shortly thereafter.97

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93 Jon Cohen, ‘I feel an obligation to be balanced’. Noted biologist comes to defense of gene editing babies, SCIENCE (Nov. 28, 2018), https://www.sciencemag.org/news/2018/11/i-feel-obligation-be-balanced-noted-biologist-comes-defense-gene-editing-babies (accessed Feb. 28, 2019).

94 Victor Dzau, Marcia McNutt, and Chunli Bai, Wake-up call from Hong Kong, 362 SCIENCE 1215 (Dec. 2018).

95 Nie, supra note 62 (‘In the Chinese context, the declaration that his project would make China the world’s first in this area is too obvious to be mentioned directly. Indeed, an initial short report of He’s research appeared on the website of chief official newspaper People’s Daily on Nov. 26, titled ‘The World’s First Gene-edited Babies Genetically Resistant to AIDS Were Born in China’. It hailed He’s venture as ‘a milestone accomplishment China has achieved in the area of gene-editing technologies’ (italics added). While still available on other websites, the report was soon removed, possibly due to the international as well as domestic outcry’).

96 Akshat Rathi and Echo Huang, More than 100 Chinese scientists have condemned the CRISPR baby experiment as ‘crazy’, QUARTZ (Nov. 26, 2018), https://qz.com/1474530/chinese-scientists-condemn-crispr-baby-experiment-as-crazy/ (accessed Mar. 12, 2019).

97 Ma Danmeng, Mao Kexin, Coco Fend, and Noelle Mateer, Baby Gene-Editing Breakthrough Claim Slammed, CAIXIN (Nov. 26, 2018), https://www.caixinglobal.com/2018-11-26/baby-gene-editing-breakthrough-claim-slammed-101352172.html (accessed Feb. 28, 2019); Christian Shepher and John Ruwitch, Scientists, officials in China abhor gene editing that geneticist claims, REUTERS (Nov. 26, 2018), https://www.reuters.com/article/us-health-china-babies-genes-letter/scientists-officials-in-china-abhor-gene-editing-that-geneticist-claims- idUSKCN1NW0A7; Elizabeth Cheung, Chinese expert in bioethics slams mainland scientist He Jiankui who claims to have created the world’s first gene-edited children, SOUTH CHINA MORNING POST (Nov. 27, 2018), https://www.scmp.com/news/hong-kong/health-environment/article/2175273/chinese-expert-bioethics-slams-mainland-scientist (accessed Feb. 28, 2019).
The government immediately announced on Nov. 26 that there would be an investigation and suggested several (fairly vague) regulations that He’s work may have violated. On Nov. 29, the Vice Minister of Science and Technology called for the suspension of any work at He’s lab. The Vice Minister for Industry and Information Technology announcing a ‘zero tolerance’ policy and barred He from competing for an award for which he had been nominated.

After He left the Summit, his location was unknown for some time. While rumors flew, including one that he had been executed, he was seen at the end of December in an apartment building at his university, SUSTC. Many said he was under the equivalent of house arrest, although William Hurlbut says He assured him that was not true and he was free to come and go. In any event, He did not use the freedom he had, if any, to make any further public statements about his experiment or his situation.

Various commentaries proliferated through the following eight weeks, with different perspectives and different analyses, but almost never with new information—until Monday, Jan. 21, at about 6:30 p.m. in China. At that time, Xinhua, the official Chinese news agency, posted a story on XINHUANET, in English, entitled ‘Guangdong releases preliminary investigation Result of Gene-Edited Babies’. It was based on an interview by Xinhua with one the investigation team’s members. The short article, under 350 words, confirmed the existence of Lulu and Nana and described some of the findings of the investigation.

The article starts, ‘A preliminary investigation into the claimed ‘genetically edited babies’ shows that Chinese researcher He Jiankui had defied government bans and conducted the research in the pursuit of personal fame and gain’.

An investigation team from Guangdong Province announced He had ‘intentionally dodged supervision, raised funds and organized researchers on his own to carry out the human embryo gene-editing intended for reproduction, which is explicitly banned by relevant regulations’. (Guangdong is the province that includes the city of Shenzhen, which is near the southern border with Vietnam.)

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98 Antonio Regalado, The Chinese scientist who claims he made CRISPR babies is under investigation, MIT TECH. REV. (Nov. 26, 2018), https://www.technologyreview.com/s/612466/the-chinese-scientist-who-claims-he-made-crispr-babies-has-been-suspended-without-pay/ (accessed Feb. 28, 2019).
99 Lily Kuo, Work on gene-edited babies blatant violation of the law, says China, THE GUARDIAN (Nov. 29, 2018), https://www.theguardian.com/science/2018/nov/29/work-on-gene-edited-babies-blatant-violation-of-the-law-says-china (accessed Feb. 28, 2019).
100 Matthew Campbell, China Shrinks From the Gattaca Age, BLOOMBERG (Dec. 5, 2018), https://www.bloomberg.com/news/articles/2018-12-05/china-fiercely-decries-he-jiankui-s-human-gene-editing (accessed Mar. 12, 2019).
101 David Grossman, The Infamous CRISPR Baby Scientist Is Missing, POPULAR MECHANICS (Dec. 3, 2018), https://www.popularmechanics.com/science/health/a25383837/crispr-baby-scientist-he-missing/ (accessed Feb. 28, 2019).
102 Elsie Chen and Paul Mozur, Chinese Scientist Who Claimed to Make Genetically Edited Babies Is Kept Under Guard, THE NY. TIMES (Dec. 28, 2018), https://www.nytimes.com/2018/12/28/world/asia/he-jiankui-china-scientist-crispr-editing.html (accessed Feb. 28, 2019).
103 Sharon Begley, ‘CRISPR babies’ scientist: ‘I’m actually doing quite well’, STAT (Jan. 9, 2019), https://www.statnews.com/2019/01/09/crispr-babies-scientist-im-actually-doing-quite-well/ (accessed Feb. 28, 2019).
104 XINHUANET, supra note 31. I have been told that the article in Chinese is a little longer, the equivalent of about 500 words in English. I am seeking to find a translation.
105 David Cyranoski, CRISPR-baby scientist fired by university, NATURE NEWS (Jan. 22, 2019), https://www.nature.com/articles/d41586-019-00246-2 (accessed Feb. 28, 2019).
where He’s university and the hospital that allegedly gave ethics permission for the experiment is located.) According to Xinhua, the experiment ran from Mar. 2017 to Nov. 2018, and He recruited eight participant couples ‘with a fake ethical review certificate’. The article says, ‘As HIV carriers are not allowed to have assisted reproduction, He asked others to replace the volunteers to take blood tests....’ Five of the eight couples did not conceive, one couple withdrew, and two of the couples became pregnant, one giving birth to Lulu and Nana and the other still pregnant. The investigation found that He’s activities ‘seriously violated ethical principles and scientific integrity and breached the relevant regulations of China. Officials in charge of the investigation said, He, as well as other relevant personnel and organizations, will receive punishment according to laws and regulations and those suspected of committing crimes will be transferred to the public security department’.

As far as I can tell, the report itself has not been published, in English or in Chinese, and Chinese officials have made no further statements about He Jiankui’s likely fate—except that on the day the Xinhua article came out, SUSTC announced that he had been fired.106 It is also worth noting that the governments of China, and of Guangdong Province, might have their own interests in how He’s work, and its relationship to those governments, was portrayed. I do not think it is too cynical to suggest that the Chinese reports of the investigation (like any governments’ reports of potentially embarrassing situations) be viewed with some skepticism.

E. Before the Summit, but Undisclosed Until Afterwards

The next category of information is, in some ways, both the most interesting and the most disturbing. Since the revelation of the He experiment, several academics have come forward to say that they had had conversations with He in which he talked about his plans to edit human embryos for birth; some of them even knew that he had started pregnancies. Most say that they tried to dissuade him and did not know that he was planning to disregard that advice and proceed. None of these academics seems to have ‘informed’ on him.

So far, we know of at least seven such academics: scientists Mark DeWitt, Craig Mello, Steven Quake, Matthew Porteus, and Michael Deem; plus ethicist William Hurlbut and his son, Science and Technology Studies scholar Ben Hurlbut.

According to a Nov. 27 article in STAT, Mark DeWitt—a genome editing researcher at U.C. Berkeley—had coffee with He in 2016, after He reached out to him.107 They talked about technical problems in gene editing and stayed in touch, with DeWitt accepting an invitation from He to lecture at his university in Jan. 2017. In Sept. 2017, DeWitt says he was shocked when He told him in an email that he was starting a clinical trial to make edited babies. ‘I thought it was a terrible idea, with or without any kinds of approvals. I told him that. I said: ‘You’re not ready’. According to DeWitt, they met again in person for dinner in Jan. 2018, at which point DeWitt once again tried to convince He not to go forward. DeWitt continued to do so in further conversations. Dr. He notified DeWitt in early Nov. 2018 when the babies were born and sent DeWitt a

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106 Id.
107 Rebecca Robbins, UC Berkeley researcher, told of CRISPR’d baby study a year ago, warned scientist not to do it, STAT (Nov. 27, 2018), https://www.statnews.com/2018/11/27/uc-berkeley-gene-edited-babies-china/ (accessed Feb. 28, 2019).
description of the experiment, which He said he intended to submit to the NEW ENGLAND JOURNAL OF MEDICINE. DeWitt told him the piece had substantial problems. At no point did DeWitt inform anyone else, telling STAT: ‘I wasn’t sure what to do, frankly. He asked for confidentiality, and told me it was all above board on his end, so I let it be’. In 2006 Craig Mello and Andy Fire won the Nobel Prize for Physiology or Medicine for discovering RNA interference. Now a professor at the University of Massachusetts, Mello was at one point a member of the Scientific Advisory Board of one of He’s companies, Direct Genomics. On Jan. 29, 2019, the ASSOCIATED PRESS reported:

Nobel Prize winner Craig Mello of the University of Massachusetts learned about the pregnancy last April from He in a message titled ‘Success’!

‘I’m glad for you, but I’d rather not be kept in the loop on this’, Mello replied. ‘You are risking the health of the child you are editing … I just don’t see why you are doing this. I wish your patient the best of luck for a healthy pregnancy’.  

The story continued with more details:

In April, He emailed Mello: ‘Good News … the pregnancy is confirmed!’ He asked Mello to keep the news confidential.

Mello, who won a Nobel in 2006 for genetics research, expressed concern about health risks. ‘I think you are taking a big risk and I do not want anyone to think that I approve of what you are doing’, he wrote. ‘I’m sorry I cannot be more supportive of this effort, I know you mean well’.  

Mello resigned from the Direct Genomics Scientific Advisory Board on Dec. 6, 2018. There is, so far, no evidence that the company was involved in the He experiment (though sources of funding for He’s work remain unclear). Neither is there any evidence that Mello tried to report He’s work to anyone.

Steven Quake, a Stanford bioengineering professor, supervised He’s post-doc in 2011. Quake is a prodigiously creative researcher, who specializes in creating and using biomedical tools, especially for nucleic acid sequencing. One of his interests is sequencing DNA reliably from single cells; this appears to have been what He worked on in his lab. According to another ASSOCIATED PRESS story:

Quake said he had met with He through the years whenever his former student was in town, and that He confided his interest a few years ago in editing embryos for live births to try to make them resistant to the AIDS virus.

108 Candice Choi and Marilynn Marchione, AP Exclusive: US Nobelist was told of gene-edited babies, ASSOCIATED PRESS (Jan. 28, 2019), https://www.apnews.com/3f3bdc73e7c84fe685f2813510329d62 (accessed Feb. 28, 2019).

109 See https://quakelab.stanford.edu/.

110 Andrew Joseph, Rebecca Robbins, and Sharon Begley, An outsider claimed to make genome-editing history — and the world snapped to attention, STAT (Nov. 26, 2018), https://www.statnews.com/2018/11/26/he-jiankui-gene-edited-babies-china/ (accessed Feb. 28, 2019).
Quake said he gave He only general advice and encouraged him to talk with mainstream scientists, to choose situations where there’s consensus that the risks are justified, to meet the highest ethics standards and to publish his results in a peer-reviewed journal.

‘My advice was very broad’, Quake said.\(^{111}\)

An article in the MIT TECHNOLOGY REVIEW stated, without attribution or details,\(^ {112}\) ‘A much smaller number, [of academics] including Stanford’s Quake and Craig Mello … knew by the middle of last year that He had already established pregnancies’.\(^ {113}\)

On Apr. 14, 2019, the NEW YORK TIMES published a lengthy story on its front page about Quake, in which he was interviewed by TIMES reporter Pam Belluck after giving the TIMES access to all his relevant emails (some with redactions).\(^ {114}\) The story is consistent with AP story, though it provides a finer level of detail. Three of those details are particularly interesting. First, He emailed Quake in early Apr. 2018 to inform him of the pregnancy. Second, He emailed Quake to tell him of the birth sometime in mid-October. And third, in late October Quake first texted and then had a telephone conversation with someone he described as ‘an extremely prominent scientist in the field’, whom he also informed of the birth. Apart from that unnamed scientist, Quake does not appear to have informed anyone else. The article concludes quoting Quake ‘To the extent that it wasn’t obvious misconduct, what does a person in my position do? Encourage him to do it right, his research, right? I mean, that’s what I believed I was doing’.

Matthew Porteus is a stem cell researcher at Stanford with a strong interest in using CRISPR to treat people with sickle cell diseases and other genetic conditions.\(^ {115}\) He was also on the organizing committee for the Summit and, along with Robin Lovell-Badge, moderated the question and answer period following He’s presentation. The publication XCONOMY interviewed Porteus on Dec. 4, shortly after the Summit:\(^ {116}\)

[Matthew Porteus]: About nine months ago, in February, JK [He’s nickname] told me he was planning on doing this. His email said that he was in the Bay Area visiting with a graduate student of his, and they’d love to set up a time to talk.

[Xconomy]: So you met face to face?

\(^{111}\) Marilyn Marchione and Christina Larson, Could anyone have stopped gene-edited babies experiment?, ASSOCIATED PRESS (Dec. 2, 2018), https://www.apnews.com/8d79b8da09624aabbec28d1227650a66 (accessed Feb. 28, 2019).

\(^{112}\) Antonio Regalado, Stanford will investigate its role in the Chinese CRISPR baby debacle, MIT TECH. REV. (Feb. 7, 2019), https://www.technologyreview.com/s/612892/crispr-baby-stanford-investigation/ (accessed Feb. 28, 2019).

\(^{113}\) Id.

\(^{114}\) Pam Belluck, Gene-Edited Babies: What a Chinese Scientist Told an American Mentor, N.Y. Times (Apr. 14, 2019, A1), https://www.nytimes.com/2019/04/14/health/gene-editing-babies.html (accessed May 18, 2019).

\(^{115}\) See http://med.stanford.edu/porteuslab.html.

\(^{116}\) Alex Lash, ’JK Told Me He Was Planning This’: A CRISPR Baby Q&A with Matt Porteus, XCONOMY (Dec. 4, 2018), https://xconomy.com/national/2018/12/04/jk-told-me-he-was-planning-this-a-crispr-baby-qa-with-matt-porteus/ (accessed Feb. 28, 2019).
MP: Yes. He started out on his non-human primate work, that he had modified embryos and attempted to implant them into animals but gotten no pregnancies. I was like, oh, thanks for the update. Then he said, now we’ll start doing this in humans. That was shocking to me. I was totally blindsided.

I was more than chiding him. [emphasis in the original] I was berating him. I told him he was putting the entire field at risk through his reckless actions. He was in what I thought was stunned silence. But he didn’t try to defend himself. The graduate student was with him but didn’t say anything to my recollection. I hadn’t heard from him since.

Also interesting is Porteus’s answer to a question about what he would do differently:

MP: Two things: One is call other people I knew he might have been speaking to, and as a group we might have come up with a decision. And perhaps I could have reached out for advice to someone more senior who has led study commissions and academies, who understands the sociology of science, and without revealing the confidence, run the situation by them and get their feedback.

Porteus goes on to say that he is not sure what else he would or should have done. On Jan. 17, 2019, Porteus, along with William Hurlbut, appeared at an event I moderated, organized by the Stanford Center for Law and the Biosciences, which I direct. The video of that event is available online. Porteus’s comments at it are consistent with what he told XCONOMY.

William Hurlbut is an Adjunct Professor and Senior Research Scholar in Neurobiology at Stanford, where he received his MD. He has taught and worked in bioethics areas for many years, most notably as a member of President George W. Bush’s President’s Council on Bioethics, chaired (for most of its existence) by Leon Kass. He met He Jiankui at a conference at Berkeley on ethical issues in CRISPR that Hurlbut had organized with Jennifer Doudna in Jan. 2017. They continued to speak, so much so that He listed Hurlbut in the acknowledgments to his July 2017 Cold Spring Harbor Talk.

After the Summit, STAT quoted Hurlbut on several aspects of his relationship with He:118

‘I knew where he was heading and tried to give him a sense of the practical and ethical implications’, Hurlbut said. ‘But he kept returning to the good that could be done’.

He was not fully transparent with Hurlbut. When the two spoke most recently, this fall, ‘JK did not tell me that he had established pregnancies’, said Hurlbut, who believes He should have done so. ‘He didn’t reveal to me what the state of his research was, though I suspected he had either pregnancies or born babies’.

[...]

And why did He violate what many scientists consider basic research norms? ‘I can’t get into his head, but he has a very earnest desire to move the science forward’, Hurlbut said.

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117 CRISPR’d Babies, supra note 30.
118 Sharon Begley, *He took a crash course in bioethics. Then he created CRISPR babies*, STAT (Nov. 27, 2018) https://www.statnews.com/2018/11/27/crispr-babies-creator-soaked-up-bioethics/ (accessed Feb. 28, 2019).
‘My overall feeling is that he’s a well-meaning person who wants his effort to count for good’.

Still, Hurlbut said, ‘I disagree with what he did’.

Hurlbut’s discussions at the Stanford CLB event on Jan. 17 are consistent with what he told STAT in late November. The most interesting addition was Hurlbut’s comment that, after the Summit, he continued to have telephone conversations with He about once a week, for three or four hours at a time. Hurlbut apparently did not disclose his suspicions about He’s work to anyone and has not, to my knowledge, discussed his reasons.

The three Stanford academics, Quake, Porteus, and Hurlbut, were the subjects of an investigation by the university concerning their contacts with He. On Feb. 7, Regalado reported that a Stanford spokesperson had said, ‘Stanford is reviewing the circumstances around Dr. He’s interactions with researchers at the university’. Two days after the Apr. 14 TIMES article on Quake, another TIMES article revealed that Stanford had exonerated all three: Quake, Porteus, and Hurlbut. The newspaper had received a copy of a letter from Stanford to Quake to that effect. The TIMES article further said that ‘the investigation of Dr. Quake began after the president of Dr. He’s Chinese university wrote letters alleging that Dr. Quake had helped with the project’. That same day, Stanford issued its own short announcement of the results of the investigation. That statement did not name the three academics, stated that the review had been conducted by a Stanford faculty member and an outside consultant (neither named), and did not make the actual report available.

The last of the academics whom we know to have had advance conversations with He about his plans is Benjamin Hurlbut, William Hurlbut’s son. Ben Hurlbut is an Associate Professor in the School of Life Sciences at Arizona State University. William Hurlbut is generally seen as a conservative on bioethical issues, with a strong religious orientation. Ben Hurlbut is far to his father’s left. He received his Ph.D. from Harvard in 2010 in History of Science with a focus on Science and Technology Studies (‘STS’), where he worked closely with STS legend Sheila Jasanoff. Like many STS scholars, he takes a critical view of modern science and its capitalist setting.

It is not clear how often He consulted with the younger Hurlbut, or what Ben Hurlbut knew about the work. Hurlbut clearly did not approve of his work: ‘These two lives are now an experiment, a matter of scientific curiosity, which is an outrageous way to

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119 Marilyn Marchione, Stanford probes faculty ties to China gene-edited baby work, ASSOCIATED PRESS (Feb. 7, 2019), https://www.apnews.com/8480105358f64ccf98c88d1f0090a8bed (accessed Mar. 1, 2019).
120 Regalado, supra note 112 (internal quotation marks omitted).
121 Stanford Clears Professor of Helping with Gene Edited Babies Experiment, The N.Y. Times (Apr.16, 2019), https://www.nytimes.com/2019/04/16/health/stanford-gene-editing-babies.html (accessed May 18, 2019).
122 Stanford Statement on Fact-Finding Review Related to Dr. Jiankui He (Apr.16, 2019), https://news.stanford.edu/2019/04/16/stanford-statement-fact-finding-review-related-dr-jiankui/ (accessed May 19, 2019).
123 I am a Stanford faculty member, but I was not that one.
124 See https://sols.asu.edu/ben-hurlbut.
125 Clive Thompson, How To Farm Stem Cells Without Losing Your Soul, WIRED (Jun. 1, 2005), https://www.wired.com/2005/06/stemcells/ (accessed Mar. 1, 2019).
126 J. Benjamin Hurlbut, Experiment in Democracy: Human Embryo Research and the Politics of Bioethics (Columbia University Press, New York: 2017).
relate to human lives’. On the other hand, Hurlbut said about He: ‘[I]t’s wrong to call him a rogue when he’s acting in line with [a scientific culture] that puts a premium on provocative research, celebrity, national scientific competitiveness, and firsts’. (I had to point out to one reporter that this statement is not an endorsement of He as much as it is an indictment of contemporary science.) Hurlbut has written on the case and, along with Sheila Jasanoff and Krishanu Saha, is planning a ‘global observatory’ on these issues.

F. The Role of Michael W. Deem

One other American academic who knew of He’s plans needs to be mentioned: Michael W. Deem, the John W. Cox Professor of Biochemical and Genetic Engineering and Professor, Physics and Astronomy, at Rice University, as well as the Founding Director of Rice’s Program in Systems, Synthetic, and Physical Biology. Deem was He’s Ph.D. advisor. He is quoted in the first ASSOCIATED PRESS story as having worked with the He in the experiment and even to have been involved in the consent process: ‘I met the parents. I was there for the informed consent of the parents’.

That first, frank avowal of his participation in the He experiment—presumably made when he thought He (and he, Deem) would be heroes—will quite likely come back to haunt him. The complete story remains unknown, but much can be said of Deem’s role in the He fiasco, thanks largely to the dogged and diligent reporting of STAT and of reporter Jane Qiu.

After the news first broke, Rice said, ‘Regardless of where it was conducted, this work as described in press reports, violates scientific conduct guidelines and is inconsistent with ethical norms of the scientific community and Rice University’. Rice has stated that it knew nothing of his involvement in this work and that it is investigating his role.

Deem’s lawyers quickly denied that he had played a substantial role: ‘Michael does not do human research and he did not do human research on this project’.

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127 Ryan Cross, Rick Mullin, Megha Satyanarayana, and Jean-François Tremblay, As claims of CRISPR use in first gene-edited babies emerge, scientists and ethicists respond, CHEM. & ENG. NEWS (Nov. 30, 2018), https://cen.acs.org/policy/claims-CRISPR-use-first-gene/96/i48 (accessed Mar. 1, 2019).
128 Begley, supra note 118.
129 Sheila Jasanoff and J. Benjamin Hurlbut, A global observatory for gene editing, NATURE (Mar 21, 2018), https://www.nature.com/articles/d41586-018-03270-w (accessed Mar. 1, 2019).
130 See https://bioengineering.rice.edu/people/faculty/michael_deem.
131 Marchione, supra note 5.
132 I have spoken on the phone several times, occasionally at length, with Qiu and she has quoted me before on this topic, so I may be biased in her favor. For what it’s worth, I think her reporting on Deem has been exceptional.
133 Todd Ackerman, Chinese scientist, assisted by Rice professor, claims first gene-edited babies, ASSOCIATED PRESS (Nov. 26, 2018), https://www.apnews.com/94efcf56cac841639d3bc9bad8db1698 (accessed Mar. 15, 2019).
134 Andrew Joseph, Rice University opens investigation into researcher who worked on CRISPR’d baby project, STAT (Nov. 26, 2018), https://www.statnews.com/2018/11/26/rice-university-opens-investigation-into-researcher-who-worked-on-crisprd-baby-project/ (accessed Mar. 1, 2019).
135 Todd Ackerman, Lawyers say Rice professor not involved in controversial gene-edited babies research, HOUSTON CHRONICLE (Dec. 13, 2018), https://www.houstonchronicle.com/news/houston-texas/houston/article/Lawyers-say-Rice-professor-not-involved-in-13465277.php (accessed Mar. 1, 2019).
According to the *Houston Chronicle*, ‘Asked to square the seeming discrepancy between what told the AP and the lawyers’ statement], Hennessy [one of his lawyers] said the statement is all Deem’s lawyers want to say for now’.

In the first *Associated Press* story, Deem said he had been present for at least some of the consent conversations and he ‘absolutely thinks’ the prospective parents understood. Deem was also quoted, in response to questions about whether the research actually happened, as saying, ‘Of course the work occurred. I met the parents. I was there for the informed consent of the parents’.

In a subsequent *Associated Press* story, Deem defended He’s actions, saying the research team did earlier experiments on animals. ‘We have multiple generations of animals that were genetically edited and produced viable offspring, and a lot of research on unintended effects on other genes’. That ‘we’ seems at least some evidence that Deem took part in the research.

On Dec. 10, STAT reported on a He paper, submitted apparently around September on preclinical work modifying the PCSK9 gene in mouse, monkey, and human embryos, which listed Deem as one of the fourteen authors. More recently, STAT has reported that He submitted another preclinical paper in late November, this one to *Nature*, on editing the CCR5 gene. For both of these papers ‘Author Contributions’ statements say that Deem designed the project and wrote and edited the manuscript. STAT was provided one of the papers and a scientist with a copy of the other manuscript read aloud its author-contributions statement over the phone.

This later STAT article further says that He submitted another paper to *Nature* at the same time, on the He experiment, entitled ‘Birth of Twins After Genome Editing for HIV Resistance’. The paper had nine authors; He was listed first and Deem was listed as the last, or senior, author. The STAT article went on to say:

A Chinese scientist who worked on the project said Deem was more than a bystander: Deem collaborated with He on the experiment and participated as a member of the research team during meetings with several volunteers in 2017 as they were recruited and went through the informed-consent process — a crucial component of a clinical trial. Deem helped to obtain the volunteers’ consent, speaking with them through a translator, said the Chinese member of the team, who asked not to be identified because the person was not authorized to speak to a reporter.

This story also quotes Deem’s lawyers:

denying that he was ‘the lead, last, or corresponding author’ on the paper submitted to *Nature*: ‘Michael Deem has done theoretical work on CRISPR in bacteria in the past, and he wrote a review article on the physics of CRISPR-Cas. But Dr. Deem has not designed, carried out, or executed studies or experiments related to CRISPR-Cas9 gene editing – something very different’.

136 Marchione, *supra* 5.
137 Marchione, *supra* 5.
138 Marchione and Larson, *supra* note 111 (internal quotation marks omitted).
139 Begley, *supra* note 29.
140 Qiu, *supra* note 29.
141 Qiu, *supra* note 29.
The lawyers also said Deem ‘did not authorize submission of manuscripts related to CCR5 or PCSK9 with any journal’, but ‘they then acknowledged that Deem was listed as an author on all three gene-editing papers and said he had had instructed the journals to remove his name from all the manuscripts’. In seeming contrast with Deem’s prior statements, they said, ‘Dr. Deem was not in China, and he did not otherwise participate, when the parents of the reported CCR5-edited children provided informed consent’.

As a former litigator, I can appreciate ways in which the lawyers might have chosen their words carefully. ‘Designed, carried out, or executed studies or experiments’ are not the only ways to have participated in them. Deem might, for example, have drafted the papers reporting on the experiment—a useful role for (presumably) the only native English speaker among a group of authors submitting to English language journals. That Deem did not expressly ‘authorize’ submission of the manuscripts is not the same as saying they were submitted against his wishes or even against his expectations. And Deem might not have ‘participated’ when the parents of Nana and Lulu gave consent while still, as the ASSOCIATED PRESS quoted him saying, having been present at some consent sessions for other parents.

This is speculation. But these issues will likely be important for Deem. If Deem is considered to have been an actual participant in this research, instead of providing casual (disregarded) advice, there could be serious consequences for him. Although it appears none of the work took place at Rice, it is clear that universities are responsible to the U.S. federal government for work done by their faculty, wherever that work was performed. Martin Cline, the first experimenter in gene therapy, was punished by his employer, UCLA, for conducting gene therapy trials over a summer in Israel and Italy, because he had not received permission from the UCLA IRB to do the work. In fact, that IRB had declined to approve the proposed experiments at UCLA. If Deem is held to have conducted ‘human subjects research’, without Rice IRB permission, even if the research were conducted in China, Rice could face sanctions from the federal government, and Rice has the power—and, to mollify the federal government, a strong incentive—to punish Deem.

It could be that Deem was not too worried about Rice’s reaction. According to STAT, Deem gave a talk at the City University of Hong Kong in June 2018 as part of a job interview for the position of Dean of its College of Engineering. He was supposedly offered the job a few months later and had been scheduled to take office in January. Instead, the school has appointed an interim dean.

G. Cards Not Yet Played

Much remains unknown or unverified about this whole saga. Certainly, the findings from the ongoing investigations in China and at Rice will be interesting—if and when they are released. When it comes to ‘cards not yet played’, we know that He wrote and submitted one or two pieces on his experiment and others on his preclinical work. Bits and bobs about them are leaking out already; it seems likely the whole texts will not remain forever concealed.

142 Ernest Beutler, The Cline affair, 4 MOLECULAR THERAPY 396, 397 (Nov. 2001).
143 Qiu, supra note 29.
144 Qiu, supra note 29 (‘Deem’s possible involvement in the CRISPR babies experiment has led the Hong Kong university to review the contract, which is now ‘pending on the result of the investigation undergoing at the Rice University’, said the Hong Kong university’s press office’).
On Dec. 10, STAT reported that He had submitted a 55-page paper to ‘an international journal’, describing genome editing of mouse, monkey, and human embryos intended to modify the PCSK9 gene and thus confer resistance to heart disease. STAT reported that the (unnamed) journal sent the piece out for outside peer review on October 2, and that it listed He as the senior author. The paper had 13 other authors, including Michael Deem. The journal apparently rejected the paper around Nov. 17. The STAT article reported that, ‘two genome-editing experts who read it’ had serious scientific and ethical problems. A later STAT article said that the journal was *Science Translational Medicine*, a ‘second label’ of *Nature*’s biggest rival among scientific journals, *Science*.146

In late November He submitted another paper to *Nature* on his pre-clinical work, dealing not with *PSCK9* modifications but *CCR5* edits.147 At the same time, He submitted to *Nature* the paper on the babies’ birth, entitled ‘Birth of Twins After Genome Editing for HIV Resistance’. Apart from some details of the authorship, we know very little about this paper, including its status with *Nature*. The STAT reporting conflicts with certain statements made by Mark DeWitt, who said that, in early November, He had showed DeWitt a paper describing the experiment that he intended to submit to *The New England Journal of Medicine*. We cannot be sure whether this was another paper or an earlier draft of the one eventually sent to *Nature*. But if and when these pieces are eventually released, they should tell us more about the details of the experiments.

V. ASSESSING THE HE EXPERIMENT

This section is my analysis of—and critique of—the He experiment. I stand by the comments I made in November to the press, that the experiment was ‘criminally reckless’ as well as ‘grossly premature, and deeply unethical’.148 What we’ve learned since then has only strengthened my views. This would have been an unethical, and terrifying, experiment even if it didn’t involve human germline genome editing. But it did, which made it even worse.

To me, the experiment has at least five major problems: a terrible risk/benefit ratio; very questionable consent; deeply unclear approval processes; grossly inappropriate secrecy; and, finally, the violation of what was as close as possible to an international ethical consensus. I will discuss each of those five below.

A. Risk/Benefit

1. The Importance of the Risk/Benefit Balance

One of the two most basic rules for human subjects is that the likely benefits *must* justify the risks being taken. The Nuremberg Code, which emerged from an American military court’s prosecution of Germans accused of criminal human experiments during World War II, is the foundational statement of human research ethics. Its sixth principle

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145 Begley, *supra* note 29.
146 Qiu, *supra* note 29.
147 Qiu, *supra* note 29.
148 See fn. 90 and 91, *supra*.
149 Nuremberg Code, United States Holocaust Memorial Museum, https://www.ushmm.org/information/exhibitions/online-exhibitions/special-focus/doctors-trial/nuremberg-code (accessed Mar. 1, 2019).
is ‘the risks of the experiment should be in proportion to (that is, not exceed) the expected humanitarian benefits’. In addition, principle two states, ‘The experiment should aim at positive results for society that cannot be procured in some other way’, and principle five states, ‘It should not be conducted when there is any reason to believe that it implies a risk of death or disabling injury’. Seven doctors were executed as a result of those trials for committing war crimes and crimes against humanity, as at least partially encapsulated in the Code. 150

The World Medical Association (WMA), a grouping of national medical associations such as the American Medical Association in the United States, has adopted a set of ‘Ethical Principles for Medical Research Involving Human Subjects’, known generally as the Helsinki Declaration, from the location where the WMA adopted the first version of the Principles in 1961. 151 (They have since been amended in nine subsequent WMA meetings, most recently in Brazil in 2013.) The Helsinki Declaration has a section on ‘Risks, Burdens and Benefits’, which includes three principles:

16. In medical practice and in medical research, most interventions involve risks and burdens.

Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

Measures to minimize the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

The Helsinki Declaration does not have the force of law and, in any event, applies, by its terms, only to physicians.

In the United States the so-called ‘Common Rule’ governing human subjects’ research emerged over the period from 1966 to 1991. This federal regulation does have the force of law (in the United States), and it embodies most American law about human

150 The Doctors Trial: the Medical Case of the Subsequent Nuremberg Proceedings, United States Holocaust Memorial Museum, https://www.ushmm.org/information/exhibitions/online-exhibitions/special-focus/doctors-trial (accessed Apr. 1, 2019).

151 Ethical Principles for Research Involving Human Subjects, World Medical Association (Jul. 9, 2018), https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/ (accessed Mar. 13, 2019).
subjects research. The Common Rule requires that (most) human subjects research be reviewed by an Institutional Review Board that, among other things, can only approve research when:

(2) Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result... The IRB should not consider possible long-range effects of applying knowledge gained in the research (e.g., the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility.¹⁵²

It further requires that risks to subjects be minimized ‘[b]y using procedures that are consistent with sound research design and that do not unnecessarily expose subjects to risk’.¹⁵³

Although the U.S. Common Rule is not binding international law—let alone binding domestic law in China—it is a good example of the international consensus for applying research ethics rules from the Nuremberg Code, the Helsinki Declaration, and elsewhere. The He experiment grossly failed its risk/benefit requirements.

2. The Risks of the He Experiment

Anytime someone tries a new intervention in humans, it needs to be done with only the most thorough preparation—and with whatever superstitions or prayers the researchers hope may avert harm. First use in humans of a new technology is always inherently dangerous. First use in human embryos of something as powerful as CRISPR is breathholdingly frightening and not to be done lightly. Something that changes genes at the stage of a very early embryo has consequences lasting throughout the crucial nine months of embryonic and fetal development, through any eventual person’s lifetime, and potentially for the lifetimes of some or all of her or his descendants. That setting increases any relevant risks. In the case of the He experiment, those risks fall into two main groups: the risks of using CRISPR in human embryos and the risks of the particular changes planned (or made).

We know some of the risks of CRISPR in embryos. The CRISPR mechanism may make changes in the wrong places, creating so-called ‘off target’ effects that can be dangerous.¹⁵⁴ Or it may make the wrong changes in the right places, both creating the risks of harm from the unexpected edits as well as losing the potential benefits from the right changes.¹⁵⁵ It may edit only some of the cells of the embryos, resulting in ‘mosaic’ organisms, with some edited and some unedited cells, which will not have reap all (or any) of the potential benefits of the edits.¹⁵⁶ And it may make some other, unexpected changes—there is evidence that, at least in some cases, CRISPR can cause large

¹⁵² 46 CFR § 111(a)(2).
¹⁵³ 46 CFR § 111(a)(1).
¹⁵⁴ Xiao-Huit Zhang, Louis Tee, Xiao-Gang Wang, Qun-Shan Huang, and Shi-Hua Yang, *Off-target Effects in CRISPR/Cas9-mediated Genome Engineering*, 4(e264) MOLECULAR THERAPY NUCLEIC ACIDS (2015).
¹⁵⁵ Kellie Schaefer, Wen-Hsuan Wu, Diana Colgan, Stephen Tsang, Alexander Bassuk, and Vinit Mahajan, *Unexpected mutations after CRISPR-Cas9 editing in vivo*, 14 NATURE METHODS 547, 548 (May 2017).
¹⁵⁶ Xiao-Jiang Li, Zhuchi Tu, Weili Yang, and Shihua Li, *CRISPR: Established Editors of Human Embryos?*, 21 CELL STEM CELL (Sep. 2017).
deletions or duplications in DNA, with unpredictable (but almost certainly not good) effects.\textsuperscript{157}

We might have known more about some of these risks. He claimed, in his Aug. 2017 Cold Spring Harbor Laboratories talk, to have done experiments on CRISPR with mouse and monkey embryos, as well as over three hundred human embryos.\textsuperscript{158} But those results have never been published. At least some of them appear to have been submitted for publication in fall 2019, shortly before the revelation of his babies, though apparently without having been accepted or any explanation for the gap between his July 2017 talks and submission. In any event, that work could only have told us about the risks for the first six days after fertilization. This would provide some information about off-target effects, large scale deletions, and so on, but nothing about whether the CRISPR method had any continuing effects through embryonic and fetal development. It would take hundreds of carefully monitored births, lives, and deaths of mice and monkeys to give some comfort about human safety for the process. He never even claimed to have done that.

We also know that there are some risks associated with the particular modifications attempted. His goal was to disable the CCR5 gene in the embryos. No functioning CCR5 gene should mean no CCR5 receptor molecules on the surface of any of the cells of the embryo, fetus, and eventual person. CCR5 receptors are normally found on several kinds of white blood cells, not just T-cells (famous as the main target of HIV) but also macrophages, dendritic cells, eosinophils, and microglia.\textsuperscript{159} They are also reported to be present in some breast and prostate cancer cells.\textsuperscript{160} All of these cells, except the cancer cells, play crucial roles in the immune system. It is not unknown to find that people with totally disabled genes can survive and even be healthy. The human body has a great deal of redundancy and resilience. It is somewhat surprising that we tolerate CCR5 deletions since CCR5 (or its close relative, CCR2) seems to occur in a large percentage of tetrapods (mammals, birds, reptiles, and amphibians),\textsuperscript{161} which at least implies it is doing something important. But we do know that there are many people in the world who have no functioning CCR5 gene. The rate seems (as far as we know) to be highest in Northern Europeans, with one study finding the highest prevalence of 2.3% in the Faroe Islands.\textsuperscript{162} Some of those are apparently healthy middle aged and older people

\textsuperscript{157} Ha Youn Shin, Chaochen Wang, Hye Kyung Lee, Kyung Hyun Yoo, Xiaoan Zeng, Tyler Kuhns, Chul Min Yang, Teresa Mohr, Chengyu Liu, and Lothar Hennighausen, CRISPR/Cas9 targeting events cause complex deletions and insertions at 17 sites in the mouse genome, \textit{8 Nature Communications} 15464 (2017).
\textsuperscript{158} Jiankui He talking about human genome editing, supra note 17.
\textsuperscript{159} Benhur Lee, Matthew Sharron, Luis J. Montaner, Drew Weissman, and Robert M. Doms, Quantification of CD4, CCR5, and CXCR4 levels on lymphocyte subsets, dendritic cells, and differentially conditioned monocyte-derived macrophages, \textit{96 Proc. Nat’l Acad. Sci.} 5215, 5220 (1999).
\textsuperscript{160} Santos Ma˜nes et al., CCR5 Expression Influences the Progression of Human Breast Cancer in a p53-dependent Manner, \textit{198 J. Experimental Med.} 1381-1389 (2003). Daniela Sicoli et al., CCR5 Receptor Antagonists Block Metastasis to Bone of v-Src Oncogene–Transformed Metastatic Prostate Cancer Cell Lines, \textit{73 Cancer Research} 7103, 7114 (2014).
\textsuperscript{161} CCR5 or its close relative, CCR2, was found in nine out of ten tetrapod species (wallabies were the only exception), from lizards to humans, though not in any fish. Hisayuki Nomiyama, Naoki Osada, and Osamu Yoshie, Systematic classification of vertebrate chemokines based on conserved synteny and evolutionary history, \textit{18 Genes to Cells} 1, 16 (2013).
\textsuperscript{162} Ute Sollocha, Kathrin Lang, Vinzenz Lange, Irina Böhme, Alexander Schmidt, and Jürgen Sautera, Frequencies of gene variant CCR5-Δ32 in 87 countries based on next-generation sequencing of 1.3 million individuals sampled from 3 national DKMS donor centers, \textit{78 Human Immunology} 710, 717 (Nov. 2017).
so it is clear that a functioning CCR5 gene is not absolutely necessary for a reasonable quantity and quality of life.

But we do not know what other effects the absence of a functional CCR5 gene might have. Does it increase prenatal losses? Infant mortality? Young adult deaths or disability? Other problems? There is some—a little—evidence that it increases the risks to a person from West Nile Virus\textsuperscript{163} and perhaps from influenza,\textsuperscript{164} which kills about 300,000 to 650,000 people worldwide every year compared with about 940,000 who die from HIV infection.\textsuperscript{165} In China, the relevant numbers are hundreds of thousands of deaths from influenza a year\textsuperscript{166} and about 30,000 deaths per year from HIV.\textsuperscript{167}

The healthy adults known to have no functional CCR5 gene are from Northern Europe. They have a different environment, diet, set of microbial exposures, and (to some extent) other human genetic variations than people in China. Is that important? We do not know. And neither does He Jiankui.

Our knowledge of the effects of not having a functional CCR5 gene is limited in still another way. The most common source of non-functional CCR5 genes found naturally in humans is the $\text{CCR5}\Delta32$ version, with a deletion of a specific string of 32 bases in the gene’s sequence.\textsuperscript{168} He Jiankui did not successfully make this 32-base-pair deletion in either of the twins, who had other, unexpected, mutations in their CCR5 genes. These seem very likely to make those genes non-functional, but do those particular mutations have the same safety profile as $\text{CCR5}\Delta32$? We have no idea. No one has seen, let alone tested, the mutations allegedly found in those girls.

3. The Benefits of the He Experiment

Those are some known risks. There is also the possibility of unknown risks. But risks are not vetoes; they need to be weighed against the benefits to the subjects and to science.

The main benefit to the possible future children is the possibility of being free from the fear of HIV infection. Note that this does not mean free from the fear of HIV infection as a result of conception from a HIV-positive father. That risk can be easily minimized, and probably completely avoided, by washing the seminal fluid away from the sperm. Sperm do not become infected with HIV, though the fluid may carry HIV virus particles. Separate the sperm from the fluid and then fertilize the egg—through IVF

\textsuperscript{163} William Glass, David McDermott, Jean Lin, Sudkamon Lekhong, Shuk Fong Yu, William Frank, John Pape, Ronald Cheshier, and Phillip Murphy, \textit{CCR5 deficiency increases risk of symptomatic West Nile virus infection}, 203 J. EXPERIMENTAL MED. 35, 40 (Jan. 2006).

\textsuperscript{164} A. Falcon, M. T. Cuevas, A. Rodríguez-Frandsen, N. Reyes, F. Pozo, S. Moreno, J. Ledesma, J. Martínez-Alarcón, A. Nieto, and J. Casas, \textit{CCR5 deficiency predisposes to fatal outcome in influenza virus infection}, 96 J. GENERAL VIROLOGY 2074, 2078 (2015).

\textsuperscript{165} Danielle Iuliano et al., \textit{Estimates of global seasonal influenza-associated respiratory mortality: a modeling study}, 391 THE LANCET 1285, 1300 (Mar. 2018); \textit{Number of deaths due to HIV/AIDS}, World Health Organization, https://www.who.int/gho/hiv/epidemic_status/deaths_text/en/ (accessed Mar. 1, 2019).

\textsuperscript{166} Xinchun Yu, Chunfang Wang, Tao Chen, Wenyi Zhang, Huiting Yu, Yuelong Shu, Wenbiao Hu, and Xiling Wang, \textit{Excess pneumonia and influenza mortality attributable to seasonal influenza in subtropical Shanghai, China}, 17 BMC INFECTIOUS DISEASES 756 (2017).

\textsuperscript{167} China Country Profile, Centers for Disease Control, https://www.cdc.gov/globalhivtb/where-we-work/china/china.html (accessed Mar. 14, 2019).

\textsuperscript{168} John Novembre, Alison Galvani, and Montgomery Slatkin, \textit{The Geographic Spread of the CCR5 Δ32 HIV-Resistance Allele}, PLOS BIOLOGY (Oct. 2005).
or through lower tech artificial insemination—and the risk of infection at conception disappears. 169

So, the relevant benefit to the twin girls is the diminution of the risk of becoming HIV infected at some time in the future, through unprotected sex or possibly intravenous drug use. That benefit is reduced to almost nothing in this case, however, for several reasons. The benefit (from avoiding the risk of HIV infection) is small, several decades away, and can be averted (already) in other ways. The general method used by He, creating non-functional CCR5 gene variations, is known not to be complete protection against HIV infection (and death). 170 And no one knows whether the specific changes He actually made to the embryos’ CCR5 genes—which he knew about before transferring them to their mother’s uterus for possible implantation, pregnancy, and birth—protect against HIV infection or progression.

For baby girls born in late 2018, the risk of HIV infection is small and far away. Only about one person in a thousand in China is infected with HIV, a prevalence lower than that of the United States and many European countries. 171 And other preventive measures, such as safe sex or avoiding intravenous drug use, are readily available, with who knows how many more to come before the girls become sexually active, let alone before they become intravenous drug users (if ever). Their risk of HIV infection, although not zero, does not seem very great and so the benefit of avoiding it is low.

But it gets worse, in many ways. First, it turns out that not just He Jiankui, but the commenting world, jumped too quickly to the idea that people without functioning CCR5 proteins on their T-cells cannot become HIV infected. 172 Most infections occur through HIV fusing into CD4 positive T-cells. 173 The virus attaches to the CD4 protein on the surface of these cells and to another cell surface protein. Most often the second protein is CCR5, but it can be another protein called CXCR4. 174 In addition, other immune system cells, dendritic cells, can be infected with HIV both through the CD4 and CCR5 route and another route that does not require CCR5. 175 The most common strains of HIV currently infecting humans, the R5 strains of HIV-1, usually seem to need CCR5 receptors to infect both CD4 T-cells and macrophages. 176 But another HIV-1

169 Maryan Zafer, Hacsi Horvath, Okeoma Mmeje, Sheryl van der Poel, Augusto Semprini, George Rutherford, and Joelle Brown, Effectiveness of semen washing to prevent HIV transmission and assist pregnancy in HIV-discordant couples: a systematic review and meta-analysis, 105 Fertility & Sterility 645, 655 (Mar. 2016).
170 Cédric Blanpain et al., CCR5 and HIV infection, 8 Receptors Channels 19-31 (2002).
171 CIA World Factbook, https://www.cia.gov/library/publications/the-world-factbook/rankorder/2155rank.html (accessed Mar. 14, 2019).
172 I have previously published a slightly different version of this discussion of CXCR4 and HIV infection in Henry T. Greely, He Jiankui, Embryo Editing, CCR5, the London Patient, and Jumping to Conclusions, Stat (Apr. 15, 2019), https://www.statnews.com/2019/04/15/jiankui-embryo-editing-ccr5/ (accessed June 28, 2019).
173 Afam A. Okoye and Louis J. Picker, CD4+ T cell depletion in HIV infection: mechanisms of immunological failure, 254 Immunological Rev. 54, 64 (2013).
174 Tsutomu Murakami and Naoki Yamamoto, Role of CXCR4 in HIV infection and its potential as a therapeutic target, 5 Future Microbiology 1025, 1039 (2010).
175 Olivier Manches, Davor Frleta, and Nina Bhardwaj, Dendritic cells in progression and pathology of HIV infection, 35 Trends in Immunology 114, 122 (2014).
176 Laura Waters, Sundhiya Mandalia, Paul Randell, Adrian Wildfire, Brian Gazzard, and Graeme Moyle, The Impact of HIV Tropism on Decreases in CD4 Cell Count, Clinical Progression, and Subsequent Response to a First Antiretroviral Therapy Regimen, 46 Clinical Infectious Diseases 1617, 1623 (2008).
strain, X-4 HIV-1, does not use CCR5 at all but instead uses CXCR4.\textsuperscript{177} Some strains of HIV-1, dual trophic HIV-1 strains, can use either CCR5 or CXCR4.\textsuperscript{178} And HIV-2, less common and less deadly, has strains that make use of many receptor molecules in addition to CD4, not just CCR5.\textsuperscript{179}

Thus, the absence of CCR5 proteins does not prevent infection with HIV but it does greatly reduce (and possibly entirely prevent) infection of the CD4 T-cells with the R5 HIV-1 strains. The X-4 and dual trophic strains can still infect both CD4 T-cells and macrophages; even the R5 HIV-1 strains can infect dendritic cells, which can serve as a reservoir of HIV where the virus can exist, and possibly mutate, even when the CD4 T-cells are not infected.

We have good evidence for the fact that the absence of CCR5 proteins is not completely protective. In 2012, the HIV world was excited by ‘the Berlin patient’, later identified as Timothy Brown.\textsuperscript{180} Brown was HIV-infected, but also developed acute myeloid leukemia, a blood cancer. His leukemia resisted drug treatment and he needed a bone marrow transplant, substituting someone else’s blood forming cells for his own, which were producing tumor cells. The doctors in Berlin gave Brown two transplants, one in 2007 and one in 2008, from the same donor, a person who had two copies of CCR5\textsubscript{Δ32}, and the very mutation that He tried to cause in the twin girls. After a rocky treatment course, which included full body irradiation, the bone marrow transplants took, and Brown was eventually able to stop taking anti-retroviral drugs without again becoming HIV positive. He has generally been viewed as the only person to have been ‘cured’ of HIV.

In early 2019, the Berlin patient’s possible successor was announced, the (so far still anonymous) London patient.\textsuperscript{181} This patient had Hodgkin’s lymphoma, a different blood cancer, but, like Brown, had received a bone marrow transplant from a donor who had no functioning copies of the CCR5 genes. The London patient, who received his bone marrow transplant in May 2016, has now been off of anti-retroviral drugs for over 18 months with no recurrence of apparent HIV infection and has been hailed as proof that Brown was not just a fluke.\textsuperscript{182} But it was also not easy. The \textit{Washington Post} noted, ‘Despite efforts to repeat the remarkable Berlin results, researchers had failed for a decade’. The \textit{New York Times} provided more details:

\begin{itemize}
\item\textsuperscript{177} Adriel D. Weinberger, Persistence and Emergence of X4 Virus in HIV Infection, 8 \textit{Mathematical Biosci. & Eng.} 605, 626 (2011).
\item\textsuperscript{178} Shi-hua Xiang, Beatriz Pacheco, Dane Bowder, Wen Yuan, and Joseph Sodroski, Characterization of a dual-tropic Human immunodeficiency virus (HIV-1) strain derived from the prototypical X4 isolate HXBc2, 438 \textit{Virology} 5, 13 (2013).
\item\textsuperscript{179} Jacqueline D. Reeves, Sam Hibbitts, Graham Simmons, Áine McKnight, José M. Azevedo-Pereira, José Moniz-Pereira, and Paul R. Clapham, Primary Human Immunodeficiency Virus Type 2 (HIV-2) Isolates Infect CD4-Negative Cells via CCR5 and CXCR4: Comparison with HIV-1 and Simian Immunodeficiency Virus and Relevance to Cell Tropism In Vivo, 73 J. \textit{Virology} 7795, 7804 (1999).
\item\textsuperscript{180} Jon Cohen, Has a second person with HIV been cured?, \textit{Science} (Mar. 4, 2019), \url{https://www.sciencemag.org/news/2019/03/has-second-person-hiv-been-cured} (accessed Mar. 15, 2019).
\item\textsuperscript{181} Ravinda K. Gupta, et al., HIV-1 Remission Following CCR5\textsubscript{Δ32}/Δ32 Haemopoietic Stem Cell Transplantation, \textit{Nature} (Mar. 5, 2019), \url{https://doi.org/10.1038/s41586-019-1027-4} (accessed Mar. 12, 2019).
\item\textsuperscript{182} Carolyn Y. Johnson, A decade after the first person was cured of HIV, a second patient is in long-term remission, \textit{The Wash. Post} (Mar. 5, 2019), \url{https://www.washingtonpost.com/health/2019/03/05/decade-after-first-person-was-cured-hiv-second-patient-is-long-term-remission/} (accessed Mar. 12, 2019).
\end{itemize}
Once it became clear that Mr. Brown was cured, scientists set out to duplicate his result with other cancer patients infected with H.I.V.

In case after case, the virus came roaring back, often around nine months after the patients stopped taking antiretroviral drugs, or else the patients died of cancer. The failures left scientists wondering whether Mr. Brown’s cure would remain a fluke.\(^{183}\)

The TIMES continued:

One important caveat to any such approach is that the patient would still be vulnerable to a form of H.I.V. called X4, which employs a different protein, CXCR4, to enter cells. ‘This is only going to work if someone has a virus that really only uses CCR5 for entry — and that’s actually probably about 50 percent of the people who are living with H.I.V., if not less’, said Dr. Timothy J. Henrich, an AIDS specialist at the University of California, San Francisco.

Even if a person harbors only a small number of X4 viruses, they may multiply in the absence of competition from their viral cousins. There is at least one reported case of an individual who got a transplant from a delta 32 donor but later rebounded with the X4 virus. (As a precaution against X4, Mr. Brown is taking a daily pill to prevent H.I.V. infection.)

The NATURE article reporting the London patient specifically discusses that ‘one reported case’, the so-called ‘Essen patient’.

The only other case of an HIV-infected patient transplanted with CCR5\(\Delta32/\Delta32\) cells who interrupted ART [anti-retroviral therapy] was the ‘Essen Patient’. In this case in which ART was interrupted one week before allo-HSCT [hemopoietic stem cell transplant from another person, ‘allo’], a rapid viral rebound of a pre-existing minority HIV-1 variant able to infect cells via the alternative CXCR4 co-receptor was observed three weeks later.\(^{184}\)

The Essen patient later died from a recurrence of the lymphoma that had required the stem cell transplant.\(^{185}\) As the wording of the quotation from the NATURE implies, some other HIV-infected cancer patients have received CCR5\(\Delta32\) transplants and survived, but they have continued on their anti-retroviral therapy so it is not known whether the drugs or the transplant has kept their HIV levels low.

The key takeaway is that CCR5\(\Delta32\) does not guarantee immunity to HIV infection and possible death. It only works for strains of HIV-1 that use only CCR5 as a co-factor along with CD4 to infect T cells. A few reporters seem to have noticed, or at least commented, on the importance of CXCR4, including early news stories from the

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\(^{183}\) Apoorva Mandavilli, H.I.V. Is Reported Cured in a Second Patient, a Milestone in the Global AIDS Epidemic, The N.Y. Times (Mar. 4, 2019), https://www.nytimes.com/2019/03/04/health/aids-cure-london-patient.html (accessed Mar. 12, 2019).

\(^{184}\) Gupta, supra note 180 (references omitted).

\(^{185}\) Lambros Kordelas, et al., Shift of HIV-1 Tropism in Stem Cell Transplantation with CCR5 Delta 32 Mutation, 371 NEW ENG. J. MED. 880 (2014); see also https://www.projectinform.org/glossary/essenberlin-patient/.
ATLANTIC, 186 NATURE, 187 and BLOOMBERG. 188 But those facts then largely disappeared, probably because ‘complete’ protection against HIV infection made for a better story, a better dilemma, and a better thought experiment, even though that it did not match the reality of the situation for the two baby girls.

Even that limited benefit—resistance to infection from R5 strains of HIV-1—may not apply to these children. He Jiankui’s slides showed that the twin he called Nana only had CCR5 edited on one of her two chromosomes. Many people, especially in Northern Europe, have one normal copy of CCR5 and one copy of CCR5Δ32. They are somewhat resistant to infection and their disease progresses more slowly—but they still can become infected and die from HIV. Nana is like them in that she has only one normal copy of CCR5. Her other copy of the gene is not CCR5Δ32 but one or more novel variants of unknown effects, either for safety or for resistance to HIV infection.

Her sister, called Lulu by He, has such previously unknown variants for both of her copies of CCR5. These variants do seem likely to prevent production of functional CCR5 protein and hence seem likely to resist infection, but biology is complicated, and we do not know for sure. Of course, we could have gotten some good evidence about this question. A researcher could use CRISPR to edit human T-cells in the laboratory (not in an embryo or a person) to have those abnormal CCR5 variants. The researcher could then test in the laboratory whether and to what extent HIV-1, either the R5 strain or the X4 strains, infected them. That would have been a good step to take before making human babies with that DNA. It is beyond ‘too bad’ that He Jiankui did not stop to try it. As it is, any possible benefits to Nana or Lulu from HIV resistance, let alone immunity, are deeply unclear.

Finally, one other possible benefit from editing CCR5 needs to be discussed. Antonio Regalado has suggested that by modifying CCR5, He might have inadvertently changed, and enhanced, the girls’ brains. 189 Some research has shown that mice with non-functional CCR5 had improved memories; 190 other new research showed that people with one copy of CCR5Δ32 recovered more quickly from strokes. 191 It is worth noting both that stroke recovery is not the same as cognitive enhancement and that

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186 Yong, supra note 73; see also Ed Yong, A Reckless and Needless Use of Human Gene Editing on Human Embryos, The Atl., (Nov. 26, 2018), https://www.theatlantic.com/science/archive/2018/11/first-gene-edited-babies-have-allegedly-been-born-in-china/576661/ (accessed May 20, 2019).

187 David Cyranoski and Heidi Ledford, Genome Edited Baby Claim Provokes International Outrage, N ATURE (Nov. 26, 2018), https://www.nature.com/articles/d41586-018-07545-0 (accessed May 20, 2019).

188 John Lauerman and Naomi Kresge, Gene-Edited Twins in China Still Face the Risk of HIV Infection, (Nov. 27, 2018) https://www.bloomberg.com/news/articles/2018-11-27/gene-edited-twins-in-china-still-face-risk-of-hiv-infection (accessed May 20, 2019).

189 Regalado, supra note 16.

190 Zhou et al., CCR5 is a Suppressor for Cortical Plasticity and Hippocampal Learning and Memory, eLife 2016;5:e20985. DOI: 10.7554/eLife.20985

191 Mary T. Joy, et al., CCR5 Is a Therapeutic Target for Recovery after Stroke and Traumatic Brain Injury, 176 Cell 1143 (2019), https://www.cell.com/cell/fulltext/S0092-8674(19)30107-2 (accessed Mar. 12, 2019). Regalado’s article notes that the study, which looked at patients in Tel Aviv, had some data showing the people with one CCR5Δ32 allele had obtained more education than those with two normal copies. This was not a finding of the paper and, in light of other significant differences between the two groups – notably that nearly 90% of the patients with the rare allele were of Ashkenazic ancestry compared with only 57% of those without that gene version – that evidence seems very susceptible to cultural or other interpretations.
none of the stroke subjects had two non-functional copies of CCR5. The evidence of benefit in stroke recovery, if any, applies only to Nana.

Regalado says there is no evidence that He set out to modify the children’s brains. Regalado contacted the key researchers on this topic, and He had never contacted them for information, as he had contacted researchers on HIV and CCR5 and PCSK9 and heart disease. And, Regalado reported, He himself said, in the question and answer period in Hong Kong. ‘I saw that paper, it needs more independent verification’…. I am against using genome editing for enhancement’. Regalado further quoted the reaction of one the scientists studying brain effects of CCR5, Alcino Silva from UCLA:

Could it be conceivable that at one point in the future we could increase the average IQ of the population? I would not be a scientist if I said no. The work in mice demonstrates the answer may be yes…. But mice are not people. We simply don’t know what the consequences will be in mucking around. We are not ready for it yet.

Silva also said that when he learned of the birth of twins, ‘My reaction was visceral repulsion and sadness’. 192

Any unintended and deeply uncertain improvements in the cognition of the twins cannot be counted as a benefit in an ethical assessment of He’s experiment. Quite the opposite: the possibility of any brain effects should be considered yet another risk of the work.

What about the benefits to science? The fact that apparently healthy children could be born after embryo editing is, certainly, a novel finding of some value. Given earlier successes with monkeys, as well as other mammals, it is not deeply surprising—but neither was it completely certain. Even closely-related species sometimes differ markedly in reproduction and early development.

But we would not yet weigh that benefit, relatively small in my view, against the risks. Remember, the Common Rule further requires that risks to subjects are minimized by ‘using procedures that are consistent with sound research design and that do not unnecessarily expose subjects to risk’. The He experiment did not have a sound research design, at least in that there was no published or otherwise generally available evidence from non-human trials about the safety of both CRISPR, in general, or about the safety of CCR5 inactivation, in particular.

4. The (Im)balance

To me, the balance is easy to weigh. The risks to the babies who might be born from the embryos grossly outweighed the almost-zero benefits to them and the relatively small benefits to science. It seems to me that no reasonable reviewing body—or researcher, who primarily carries this ethical obligation—could find otherwise.

These considerations of risk/benefit balance become all the more important in the context of this particular research—research not just on persons who cannot consent, but on embryos that are not yet persons and cannot consent. If a mentally-competent adult suffering from a dread disease decides to try a very risky experimental treatment and things go wrong, at least she had made a voluntary and, presumably informed, choice to take those risks. In He’s experiment, the prospective parents certainly bore

192 Regalado, supra note 16.
some risks, but most of the risk directly fell on any embryos that became babies. Those embryos never got a chance to consent.

I do not want to belabor this. Neither I nor, I strongly suspect, you, dear reader, gave consent to being born—let alone to whom, where, and when you were born. We do, and must, allow children, fetuses, and embryos intended for implantation to be research subjects without their own personal informed consent in order to learn how best to treat them.

But the Common Rule has special requirements for such research. Its Subpart B applies to fetuses (defined as any product of conception after implantation) as well as pregnant women and neonates. Subpart D applies specifically to research with children. Neither applies to ex vivo embryos, but the reasons for the special requirements apply equally there. The provisions protecting embryos and children are similar, but are spelled out most cleanly in Subpart D, about children. It provides:

HHS will conduct or fund research in which the IRB finds that more than minimal risk to children is presented by an intervention or procedure that holds out the prospect of direct benefit for the individual subject... only if the IRB finds that:

(a) The risk is justified by the anticipated benefit to the subjects;
(b) The relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternative approaches; and
(c) Adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians....

If Subpart D applied to He’s experiment (which is does not, both because there is no connection to the U.S. Department of Health and Human Services and because embryos are not ‘children’), it would clearly classify this research as more than minimal risk. It seems to me that even the claimed anticipated benefit cannot justify the risks. It is even more clear, though, that the ratio of the benefit (possibly reducing the risk of HIV infection in the distant future) to the risk from this unprecedented experiment is far worse than alternative ways to prevent any resulting humans from being infected with HIV.

If the research involves more than minimal risk, and there is no anticipated benefit to the child, the Subpart states:

HHS will conduct or fund research in which the IRB finds that more than minimal risk to children is presented by an intervention or procedure that does not hold out the prospect of direct benefit for the individual subject, or by a monitoring procedure which is not likely to contribute to the well-being of the subject, only if the IRB finds that:

(a) The risk represents a minor increase over minimal risk;
(b) The intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations;

193 46 C.F.R. 46.201 et. seq. ‘Fetus’ is defined in 46 C.F.R. §206.202(c).
194 46 C.F.R. Subpart D, §§46.101 et seq.
195 46 C.F.R. §46.405.
(c) The intervention or procedure is likely to yield generalizable knowledge about the subjects’ disorder or condition which is of vital importance for the understanding or amelioration of the subjects’ disorder or condition; and

(d) Adequate provisions are made for soliciting assent of the children and permission of their parents or guardians.  

Subsections (b), (c), and (d) do not seem to be satisfied here, but the main problem is that this research is clearly more than ‘a minor increase over minimal risk’.

So, assuming Subpart D applied, what is left? Section 46.407.

HHS will conduct or fund research that the IRB does not believe meets the requirements of §46.404, §46.405, or §46.406 only if:

(a) The IRB finds that the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children; and

(b) The Secretary, after consultation with a panel of experts in pertinent disciplines (for example: science, medicine, education, ethics, law) and following opportunity for public review and comment, has determined either:

1. That the research in fact satisfies the conditions of §46.404, §46.405, or §46.406, as applicable, or

2. The following:

   (i) The research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children;
   
   (ii) The research will be conducted in accordance with sound ethical principles;
   
   (iii) Adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians, as set forth in §46.408.

Might the He experiment have qualified under this provision? I think it fails almost every provision of §46.407(b)(2)—but, of course, Subpart D did not apply. It does serve, though, to show that higher standards about risk and benefit will be applied to children—and presumably to embryos that, like children, cannot consent for themselves.

Another point is worth noting. Under the Common Rule, in the United States, IRBs are expressly forbidden to ‘consider possible long-range effects of applying knowledge gained in the research … as among those research risks that fall within the purview of its responsibility’[emphasis added]. That’s the binding American law; it is not necessarily an appropriate ethical condition. I don’t think anyone needs to reach this question in the case of the He experiment, because even on a restricted view of the risks, they hugely outweigh the benefits. But, certainly, many people do think the ‘possible long-range effects’ of human germline genomic editing include very substantial risks.
So far I have discussed weighing the balance of risk and benefit before the start of the He experiment. But both the Helsinki Declaration and the U.S. Common Rule require that the risks to human subjects be minimized, which the Helsinki Declaration at least makes clear is a continuing duty (something I think is also true, but less explicit, in the Common Rule). ‘Measures to minimize the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher’. 199

He Jiankui says that he examined the DNA of the embryos that became the twins before making a decision to transfer them into their mother’s uterus. At that time, he knew that he had failed to make the change he wanted, from a normal CCR5 gene to CCR5Δ32. So he knew then both that the risks would be higher, because the edited versions of the gene had not been seen in humans, and that the benefits would be more uncertain. Even in the unlikely event someone concluded the experiment’s balance of risks and benefits had been appropriate in advance, once it became clear that the planned edits had not been made, that calculus would change. And the continuing duty to monitor and assess risks would have prohibited the transfer of those embryos for possible birth.

B. Questionable Consent

Along with a favorable risk/benefit ratio, proper consent is at the top of the list of requirements for ethical human subjects’ research. He’s experiment seems quite likely to have failed that as well, for several reasons.

First, the consent process itself was flawed. George Annas from Boston University described it as more of a ‘contract’ than a ‘consent form’. 200 Its very first sentence says ‘The research team is launching an AIDS vaccine development project’. 201 Although one can see a parallel between genomic editing to provide immunity to HIV infection and the injection of an actual vaccine, that’s an analogy, not an identity. To call embryo editing, which had never been used before in an attempt to lead to human babies, a ‘vaccine’, a ubiquitous and widely accepted procedure, is deeply misleading.

The whole form is 23 pages, although the last 13 are technical annexes of little value to potential patients. The form does discuss CCR5 and gene editing on the first page, but in a highly technical manner. As the primary benefit to the parent, it says (optimistically) ‘This research project will likely help you produce HIV-resistant infants’.

The form for the mothers begins in Article 2 by detailing the risks to the woman of the medical procedures she will undergo. Article 3 largely disclaims responsibility for these risks, specifically disclaiming liability for any risks that the woman will become infected with HIV or any other infectious disease, or that the children will not be

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199 Declaration of Helsinki, Principle 17.
200 George J. Annas, How Did Claims of CRISPR Babies Hijack an International Gene-Editing Summit?, Boston University School of Public Health (Dec. 4, 2018), https://www.bu.edu/sph/2018/12/04/how-did-claims-of-crispr-babies-hijack-an-international-gene-editing-summit/ (accessed Mar. 15, 2019). The form itself can no longer be reached at the Chinese site where it was first posted, that for the Southern University of Science and Technology, He’s (former) employer, but thanks to the ‘Wayback Machine’, a copy of what purports to be an English translation of the consent form of the women (not as far as I can tell for the men) is available on a web archive at http://web.archive.org/web/20181126212007/http://www.sustc-genome.org.cn/source/pdf/Informed-consent-women-English.pdf.
201 Derek Lowe, After Such Knowledge, IN THE PIPELINE (Nov. 28, 2018), https://blogs.sciencemag.org/pipeline/archives/2018/11/28/after-such-knowledge (accessed Mar. 1, 2019).
HIV-resistant. The third paragraph of Article 3 contains the only discussion of the risk to any children of the gene editing process:

The primary risk of gene editing (DNA-targeted CRISPR-Cas9 endonuclease) is the off-target effect of generating extra DNA mutations at sites other than the intended target. This is due to that the technique can cause nonspecific cleavage, resulting in mutations in non-targeted genomic sites. PGD, whole genome-wide sequencing, amniocentesis and peripheral blood test of mothers in different stages of pregnancy after transplantation will minimize the possibility of substantial injury. Therefore, this project team is not responsible for the risk of off-target which is beyond the risk consequences of the existing medical science and technology.

Damningly, at no point does the document note that this technique has never before been used to try to make human babies.

There are other interesting provisions in the ‘consent form’. The seventh paragraph in Article 2 says:

Regarding the qualitative characterization of the project results, only the project team has the right of final interpretation and announcement to the public. Then you have NO right to explain and have NO right to announce the project or result information without permission. Violation of this will dealt as breach of contract and the volunteers need compensate for the damages (The specifics are defined in the liquidated damages cooperation agreement).

The document makes a similar statement in Article 10: ‘Regarding the project results, only the project team has the right of final explanation and announcement to the public. The volunteers have no right to explain, publish, or announce project related information without permission’.

The prospective research volunteers are given a free chance to withdraw from the research only up to a point.

After the embryo implantation in the first cycle of IVF until 28 days post-birth of the baby, if you decide to leave the study due to other reasons than the ones listed in Items 3 and 4 above,[202] you will need to pay back all the costs that the project team has paid for you. If the payment is not received within 10 calendar days from the issuance of the notification of violation by the project team, another 100,000 RMB of fine will be charged.

Article 7, Section 2 of the document estimates that the project team will have to spent 280,000 RMB on each research couple, mainly for the medical procedures. This is about $40,000, a huge sum for most Chinese couples (or American couples for that matter) to pay even before the additional 100,000 RMB fine.

The document describes the research procedures as trade secrets, forbids the subjects from disclosing them, and says they may not ‘use the secret through reverse engineering’. Needless to say, this is a very odd provision in a consent form for a non-scientist, non-physician, hopeful mother to sign.

202 These refer to the failure to become pregnant or sustain a pregnancy after two efforts or the aftermath of a pregnancy where the embryo or fetus has ‘genetic defects or other serious disease’.
The consent form seems grossly inadequate—as well as downright odd. Now, it is possible that the form did not accurately reflect the discussions held between the researchers and the prospective parents; maybe they got a fuller description. He says he spent an hour and ten minutes describing the procedures to at least some of the prospective parents. Michael Deem told the Associated Press that he attended at least some of the consent sessions and that he was confident in the parents’ ability to understand the risks.

On the other hand, we have no other reports on what the consent sessions were like. At the Summit, He claimed that the prospective parents were all well-educated; some dispute this. It is clear that neither He nor Deem, nor, apparently, anyone else involved, had been trained on the processes of informed consent.

And, perhaps most powerfully, another problem with consent has slowly emerged. Why would parents choose to do a ‘never before done in humans’ gene edit to make their babies? He said at the Summit that parents with HIV, facing what is a strong stigma in China, were eager to avoid the possibility that, at some remote time in the future, their children could become infected. It is possible that they mistakenly thought that only the gene editing could prevent the prenatal transmission of HIV to the children, even though sperm washing could accomplish the same end with no risks.

But there is another, chilling, possibility. It may be difficult, expensive, and perhaps illegal and impossible for many people in China who are HIV positive to use the kind of assisted reproductive services that could include sperm washing. It is not clear that these services are available for HIV-positive couples. The Xinhua report of the Guangdong province investigation says that, ‘HIV carriers are not allowed to have assisted reproduction’. So it may be illegal; if not illegal, it would certainly be very expensive. If such a couple wanted genetic children—a very strong drive in Chinese culture—they could conceive the old-fashioned way, but that would risk prenatal transmission to their children. Or, if they had a lot of money, they could seek IVF, though this would possibly be illegal. Or they could accept the offer to join He’s experiment and not only receive IVF, but receive it for free alongside various other reimbursements. Dr. Kathy Niakan, one of the researchers who spoke right before He in Hong Kong said, ‘Offering vulnerable patients free IVF treatment presents a clear conflict of interest’. This looks like ‘undue inducement’—the notion that people should not be lured, bribed, or coerced into taking part in research. ‘Undue inducement’, as a concept, has been criticized, with some justice. But at a certain point ‘take part in my experiment

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203 Session 3, supra note 81.
204 Marchione, supra note 27.
205 Session 3, supra note 81.
206 Christopher VanLang, Should the twin babies that Chinese scientist He Jiankui gene-edited be able to sue him, and possibly their parents as well, for altering their DNA?, Quora (Dec 3, 2019), https://www.quora.com/Should-the-twin-babies-that-Chinese-scientist-He-Jiankui-gene-edited-be-able-to-sue-him-and-possibly-their-parents-as-well-for-altering-their-DNA (accessed Mar. 15, 2019).
207 Session 3, supra note 81.
208 XINHUANET, supra note 31.
209 Suzanne Statline and Ian Sample, Scientist in China defends human embryo gene editing, The Guardian (Nov. 28, 2018), https://www.theguardian.com/science/2018/nov/28/scientist-in-china-defends-human-embryo-gene-editing (accessed Mar. 12, 2019).
210 Ezekiel Emanuel, Ending Concerns About Undue Inducement, 32 J. LAW, MED. & ETHICS 100, 105 (2004).
or I’ll kill your child’ is unethically coercive. When the inducement is ‘take part in my experiment as it is your only hope of having children without having a high risk of infecting them with HIV’, the idea that this is unfair seems quite strong—and the appropriateness of He’s ‘informed consent’ in this case becomes even more questionable. This may be viewed as particularly true in a culture, like Chinese traditional culture, where having children to carry on the family (and especially boys to carry on the family name) is very highly desired.

C. A Very Questionable Approval Processes

It is not clear whether He got any permission from anyone for his experiment. His own university, Southern University of Science and Technology, says it knew nothing about the experiment, which He echoed at the Summit. It appears that the assisted reproductive centers, seemingly at four different hospitals, also claim not to have known what he was doing or to have approved it.

He said the Shenzhen Harmonicare Women’s and Children’s Hospital provided the ethics committee, the equivalent of an IRB, that had approved the project. The original Associated Press article quoted Lin Zhitong, whom it described as ‘a Harmonicare administrator who heads the ethics panel’ as saying ‘We think is ethical’. On the other hand, after the reveal, that hospital released a statement saying ‘the Medical Ethics Committee never met to discuss such a project, and that the signatures on He’s approval form ‘are suspected to have been forged’ In a Nov. 27 statement, Harmonicare said it ‘will invite public-security organizations to participate in the investigations and pursue the legal responsibilities of the relevant individuals’. The January Xinhua article on the Guangdong provincial investigation stated that He recruited subjects ‘with a fake ethical review certificate’. It is, of course, possible that the hospital is trying to cover up its role and the investigation did not detect, or even allowed, the deception—we have little clearly reliable evidence for this, as for so much of the He Jiankui story.

Even more interestingly, that article reports that ‘As HIV carriers are not allowed to have assisted reproduction, He asked others to replace the volunteers to take blood’. If, in fact, He violated Chinese law by procuring assisted reproduction for HIV carriers through recruiting uninfected men who would then provide blood for testing while falsely claiming to be the research subjects, that kind of fraud on an approval process should be actionable anywhere. The fact that the rule He allegedly circumvented may be an unjust one cannot here excuse his fraud.

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211 Southern University of Science and Technology Statement On the Genetic Editing of Human Embryos Conducted by Dr. Jiankui HE (Nov. 26, 2018), http://sustc.edu.cn/en/info_focus/2871 (accessed Mar. 1, 2019).
212 Session 3, supra note 81.
213 Rita Liao, Hospital in China denies links to world’s first gene-edited babies, TechCrunch (Nov. 26, 2018), https://techcrunch.com/2018/11/26/hospital-denies-gene-edited-babies-china/ (accessed Mar. 1, 2019).
214 Marchione, supra note 27.
215 Yong, supra note 73.
216 Campbell, supra note 100.
217 XINHUANET, supra note 31.
218 Id.
D. An Utter Lack of Transparency

The guidelines and statements about human germline genome editing have universally called for transparency, broad discussion, creation of forums, and so on. Dr. He created absolutely no public discussion of his experiment before the babies’ existence was announced. We do know that he talked to several people about the work—including at least Matthew Porteus, William and Ben Hurlbut, Steve Quake, Craig Mello, and Mark DeWitt, as well as his apparent collaborator, Michael Deem. But most of those (except Deem, who has been resolutely silent since the story broke) have said that He told them he was thinking about that kind of work—never that he was planning to do it, let alone that he had actually done it. And the exceptions learned of the pregnancies only after they were established. Several advised He not to proceed, at least at this time.219

The robust discussion envisioned by various committees and others was nowhere to be seen. The He work was done in secrecy, although, clearly, He was planning about how to disclose it to make world news. He had five YouTube videos ready to put on the Internet on Nov. 25, when the Regalado article first breached his cone of silence. The ASSOCIATED PRESS had interviewed He in depth, clearly with his permission, and (I suspect) in keeping with He’s plan to use the ASSOCIATED PRESS story to help introduce his experiment—and babies—to the world. Dr. He was not trying to avoid discussion entirely, but he was trying to avoid discussion before his experiment was ready to reveal, and to control the discussion in ways favorable to himself.

E. Violating an International Ethical (Near) Consensus

Statements from organizing committees, national academies, and nonprofit bioethics organizations are not law. But they do represent important consensus. The U.S. Declaration of Independence frames itself as something required by ‘a decent respect to the opinions of mankind’. The ‘opinions of mankind’ were well represented in various statements before He’s announcement about human germline genome editing. One should not fly in their face without good reasons. But, for reasons that seem focused on his own future fame, He did.

The most relevant statements are the early SCIENCE and NATURE opinion pieces; the summary statement from the First International Summit; and, most importantly, the Feb. 2017 National Academies report and the July 2018 Nuffield Council report. (By the time of the Nuffield report the pregnancy that led to Lulu and Nana had already begun; not so for the other documents.) The NATURE piece flatly called for a ban on human germline genome editing. The others did not call for a ban, but either said any such efforts today were premature or set out criteria that would need to be met before CRISPRing babies should be tried—criteria that were far from reality. He’s experiment disregarded them all.

Consider the two most thorough and formal statements—the reports of the National Academies and of the Nuffield Council. The first listed 10 requirements:

1. absence of reasonable alternatives;
2. restriction to preventing a serious disease or condition;

219 CRISPR’d Babies, supra note 30. Marilynn Marchione, Stanford Is Reviewing Faculty Links to Chinese Scientist Who Claims He Made Gene-Edited Babies, TIME (Feb. 7, 2019), http://time.com/5524550/stanford-faculty-links-scientist-china-gene-editing/ (accessed Mar. 1, 2019).
3. restriction to editing genes that have been convincingly demonstrated to cause or to strongly predispose to the disease or condition;
4. restriction to converting such genes to versions that are prevalent in the population and are known to be associated with ordinary health with little or no evidence of adverse effects;
5. availability of credible pre-clinical and/or clinical data on risks and potential health benefits of the procedures;
6. ongoing, rigorous oversight during clinical trials of the effects of the procedure on the health and safety of the research participants;
7. comprehensive plans for long-term, multigenerational follow-up while still respecting personal autonomy;
8. maximum transparency consistent with patient privacy;
9. continued reassessment of both health and societal benefits and risks, with broad on-going participation and input by the public; and
10. reliable oversight mechanisms to prevent extension to uses other than preventing a serious disease or condition.220

HIV infection must be counted as a ‘serious disease or condition’, although not nearly as serious as it used to be. That is, He’s experiment may have satisfied the second requirement. But it clearly violated requirements number 4, 5, 8, 9, and 10. I would argue it also violated 1 and 3, and He gave no signs of having adhered, or planning to adhere to numbers 6 and 7. The Report argued, ‘broad participation and input by the public and ongoing reassessment of both health and societal benefits and risks are particularly critical conditions for approval of clinical trials’. He not only failed to meet this condition, but his secrecy prevented any possibility of the participation and input called for.

He’s experiment similarly failed to meet the Nuffield Council’s requirements, listed above in Section III(C), Box 2. Most notably, it went forward with no wisp of the regulatory process the Council sought:

We recommend that heritable genome editing interventions should only be licensed on a case-by-case basis subject to: assessment of the risks of adverse clinical outcomes for the future person by a national competent authority (in the UK, the HFEA); and strict regulation and oversight, including long-term monitoring of the effects on individuals and social impacts.221

Of course, He could claim that he disagrees with those conditions (although, in fact, he has argued that he complied with them.) But in his ‘ethics article’ in The CRISPR Journal, published on Nov. 26, 2018, he set out his own, vague, core principles. One of them, however, was not vague: ‘Performing gene surgery is only permissible when the risks of the procedure are outweighed by a serious medical need.’222 People often will

220 Human Genome Editing: Science, Ethics, and Governance, supra note 47.
221 Nuffield Council on Bioethics, supra note 45.
222 Elizabeth Cooney, What we know – and what we don’t – about the claim of the world’s first gene-edited babies, STAT (Nov. 26, 2018), https://www.statnews.com/2018/11/26/what-we-know-gene-edited-babies-crispr/ (accessed Mar. 1, 2019).
believe what they want to believe. It is possible that He genuinely thought his experiment met that requirement. I do not see how any reasonable person could agree that the risks of doing a ‘first in human’ embryonic gene editing were outweighed by lowering any resulting person’s eventual risk of becoming infected with HIV, but, as Paul Simon wrote, ‘All lies and jest/Still, a man hears what he wants to hear and disregards the rest’.223

Even more concretely, He and his team stated, ‘we hold additional but less universal beliefs that further restrict the use of gene surgery, including … focus only on treating disease via prevalent, natural genetic variants’. This sounds to me like a restriction of ‘gene surgery’ to cases where the (rare) pathogenic variant, say a 185delAG mutation in BRCA1, is changed to the widely prevalent, ‘normal’ variant, thus avoiding the risks of a new allele. The 32-base-pair deletion in CCR5 that He attempted to create in the embryos, while ‘natural’, is nowhere ‘prevalent’ and is quite rare, if not unknown, in China, among people with the other genetic variations—and the environment, understood broadly—of the Chinese. But even if it does qualify, that would not justify He in transferring to a uterus the two embryos he did—one that did not have 32-base-pair deletion but has other mutations and one that had any changes in the gene in only one of its two copies of the gene. The experiments whose results he announced on Nov. 25 on YouTube and on Nov. 28 at the Summit violated his own ethics paper, published on Nov. 26.

VI. WHAT NEXT?—SHORT TERM RESPONSES224

The He experiment was a fiasco. We can only hope that the two babies already born do not suffer from it, either in their health or in their possible resulting notoriety. More broadly, I do think the experience has important lessons that Science must heed. Science does not have a President, Prime Minister, or Pope. But Science does have leaders, individual and institutional, and those leaders have some influence over public perceptions. Leaders reacted—but their reactions were insufficient. Now they badly need to do three things: enforce deterrence, create disclosure, and express humility. China, on the other hand, does have leaders and they need to take some specific steps—and, unlike Science, Chinese leaders seem to be well on the way to doing so.

A. What Must Science Do?

1. Enforce Deterrence

He Jiankui expected to be hailed as a hero, or at least to be seen by most as an important pioneering figure. He gambled his high-flying present for the hopes of an even higher-flying future. Thus far, he seems to have bet wrong. Far from being a hero, he has been (almost) universally condemned, and may to be facing criminal prosecution in China. But whatever happens in China, Science needs to ensure he is ostracized. No future ambitious scientist should see this kind of experiment as anything but a suicidal career move.

In 1980 when UCLA’s Martin Cline violated ethical rules by pursuing the first (unapproved) gene therapy trials, he lost positions and grants; his career never recovered.

223 Paul Simon, The Boxer (1969).

224 A version of Sections A, B, and C of this part has appeared as Henry T. Greely, How Should Science Respond to CRISPR’d Babies, 35 Issues in Sci. & Tech. (2019).
Hwang Woo-Suk acted much worse by fraudulently claiming to have cloned human embryos. Until his fraud was discovered in late 2005, Hwang was a hero in South Korea, where his face graced a postage stamp. Following the revelations, Hwang was fired from his faculty position at Seoul National University, South Korea’s premier research institution; he lost all his grants; and, in 2009, he was convicted of fraud and embezzlement and given a two-year prison sentence (suspended and later reduced to 18 months). Hwang has subsequently begun to rebuild his reputation with animal cloning work, but he has never regained his previous position. Similarly, He Jiankui’s career needs to be ruined—not necessarily forever, but for a long, long time.

How should Science accomplish this? Colleagues should shun him, journals should refuse to accept papers where he is an author, funders should forsake him. He needs to be on publicly-announced blacklists, at the very least by journals and funders. And leaders of Science need to take the lead in announcing this and in encouraging others to do the same.

Of course, collective ostracism, particularly coming from official or semi-official leadership, could descend into the abyss of McCarthyism or even Stalin-era Lysenkoism. Individual scientists should decide, based on their own conscience, whether to have anything to do with He. I would encourage them to reject any contact with or overtures from He, based on what is already known. The Presidents of the National Academies and their foreign equivalents, the directors of the NIH and NSF and their foreign equivalents, while not pressuring scientists to avoid He, should make it clear that they approve the shunning of He, pending further light on the situation. Journals should take the same position. Funding agencies, particularly governmental ones, may have a harder time ignoring applications before an official determination of He’s guilt, but they should at least explore their legal powers to do so.

I do not recommend at this point that the U.S. Academies, federal research funders, or foundations that support research perform their own investigation of He’s actions. (Although investigations could well be necessary for He’s collaborator from Rice University, Michael Deem). But these groups should be alert to final determinations coming from Chinese authorities investigating the situation. Some steps have already been taken against He: his funding has been cancelled, and he has been fired from his faculty position. Chinese sources have implied that he will likely face criminal charges. Additional Chinese criminal or civil findings against him should be the basis for formal disqualification or other ‘blacklisting’, at least as long as those determinations are credible. Perhaps, someday, a long life of repentance and good works by He might justify Science in readmitting him into its ranks—but not soon, both for his own demerits and, more importantly, to ‘encourage the others’.227

225 Choe Sang-Hun, Korean Scientist’s New Project: Rebuild After Cloning Disgrace, THE N.Y. TIMES (Feb. 28, 2014), https://www.nytimes.com/2014/03/01/world/asia/scientists-new-project-rebuild-after-cloning-disgrace.html (accessed Mar. 15, 2019).

226 Sam Kean, The Soviet Era’s Deadliest Scientist Is Regaining Popularity in Russia, THE ATL. (Dec. 19, 2017), https://www.theatlantic.com/science/archive/2017/12/trofim-lysenko-soviet-union-russia/548786/ (accessed Mar. 13, 2019).

227 This is the translation of Voltaire’s line in his novel Candide on the execution of British admiral John Byng after losing the battle of Minorca. In Portsmouth, Candide witnesses the execution of an officer by firing squad and is told that ‘in this country, it is good to kill an admiral from time to time, in order to encourage the others’ Voltaire, Candide. See John Byng, WIKIPEDIA, https://en.wikipedia.org/wiki/John_Byng (accessed Mar. 1, 2019).
2. Create Disclosure (‘Snitching’)

A harder question is raised by all the academics who had hints, or direct knowledge, of what He was doing, but said nothing. This list includes at least scientists Matthew Porteus and Stephen Quake at Stanford; Mark Dewitt at U.C. Berkeley; Nobel Prize winner Craig Mello at the University of Massachusetts; and He’s collaborator, Michael Deem at Rice. It also includes father-and-son ethicists William Hurlbut at Stanford and Ben Hurlbut at Arizona State University. Each has said that he had conversations with He about human embryo gene-editing. Each has said that he discouraged He from doing it. Several have said that they suspected he might be doing it anyway. A few have said they actually knew about the pregnancies some months before the babies were revealed. Not one of them disclosed his knowledge in advance, at all, to anyone.

I think they should have. But the word ‘snitching’ conveys some of the difficulties of insisting on disclosure. Informing on others is sometimes socially required, while at the same time often socially repugnant. From siblings, to high school students, to employees, ‘informing the authorities’ about a colleague’s misbehavior will often get you labeled as a snitch. Or often as a ‘dirty snitch’.

In addition to this basic social conditioning, conventions of confidentiality in science are important for allowing colleagues to communicate without fear of being scooped. Both peer review in publications, and review in grant applications, typically includes strong confidentiality requirements, such as the destruction of any paper or electronic copies of the submitted article or the grant application. That internal code of confidentiality presumably leads to more discussion and cross-fertilization of ideas—and better research. Destroying it could slow scientific progress.

More concretely, scientists who snitch will almost certainly ruin their relationship with the ‘snitched upon’ colleague the same way pediatricians who—in good faith and in response to strong state laws—report parents as potential child abusers, will often lose those parents and their children as patients. Informing scientists might even find themselves sued—successfully or not—for libel, slander, and various other torts. If the ‘snitch’ is a competitor, as will often be the case, tortious claims might even be plausible. And the scientists who report may incur broader social costs from other colleagues and potential collaborators who shun them as snitches.

Against the backdrop of this social conditioning and the valuable conventions of confidentiality, should the scientists aware of He’s activities have disclosed their conversations and suspicions? And, if so, to whom?

This is not a new question, to science or generally. It is not even new in discussions of the He affair: an editorial in SCIENCE magazine by the presidents of three national academies called for ‘an international mechanism that would enable scientists to raise concerns about cases of research that are not conforming to the accepted principles or standards’.228

This question has arisen before in the biosciences with respect to so-called ‘dual-use technologies’, those that could be used for good purposes or for evil ones, such as biological warfare. It also comes up in more routine situations where someone is aware

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228 Dzau, supra note 94.
of wrongdoing and we as a society want to encourage or protect their whistleblowing. *Qui tam* statutes, giving whistleblowers some of the proceeds of suits against wrongdoers, date at least as far back as the Civil War. Their use has continued and expanded in recent years, especially in cases where fraud against the US government is alleged.229 And sometimes failure to ‘snitch’ on illegal activity is itself a crime, either under specific statutes, such as those concerning child abuse230 or elder abuse231, or more general criminal statutes.232

The He affair is simply the most recent example of why Science should think hard, about encouraging, or even requiring, scientists to inform someone of their concerns about on-going research. I am largely convinced that such an obligation should be created. But the details are important, and those are tricky to get right.

What would be the obligation? Only to disclose behavior you believe to be illegal, or is ‘unethical’ enough? Is this a binding legal or ethical obligation or a guideline or aspiration? Do you have to be certain of the other’s misbehavior, to have ‘clear and convincing evidence’, or to have a ‘preponderance of the evidence’, or just to have ‘reasonable suspicion?’ What kinds of things should be reported? Plagiarism? Inappropriate authorship credit or order? Minor unapproved changes in a human subjects protocol? Dangerous work? Unethical work? Illegal work?

Then we hit the question of whom to tell. At least one of He Jiankui’s confidants, Matthew Porteus, has said that he thought about telling someone about He’s likely plans, but he did not know where to go.233 This is a real problem, especially when the two scientists are not in the same institution. When they are at the same university, a word to the relevant ombudsperson, department chair, dean, research vice president, or president might do the trick. But how would, say, Stanford professor Matt Porteus go about contacting someone at China’s Southern University of Science and Technology? It is useless to tell people to gather up their courage and take action, unless you help them with suggestions of where and how to report the misbehavior of colleagues.

We should create ‘scientific snitching’ bodies. They could be located in academic institutions, in funding bodies, in national governments, or even in some kind of international organization. Scientists should be told they have a duty to report this entity some kinds of illegal, unethical, or dangerous research. Congress, or another national legislature, could even give immunity from lawsuits for those who report, when they act in good faith.

But we also should spare a moment’s thought, and pity, for the people who receive these reports. Some will be from disgruntled coworkers, or jealous rivals, or from the apparently mentally ill. How much chaff will need to be sifted to reveal how little grain? And who in the world would want that job?

At this point I am not sure exactly how ‘snitch bodies’ should work, but I am convinced that Science needs to think hard about encouraging internal reporting of dangerous, unethical, or illegal research. The alternative may well be ham-fisted

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229 David Freeman Engstrom, *Private Enforcement’s Pathways: Lessons from Qui Tam Litigation*, 114 COLUM. L. REV. 1913 (2014).

230 Such as California’s Child Abuse and Neglect Reporting Act. California Penal Code §§ 11164-11174.3.

231 See, e.g., California Penal Code § 368.

232 See, e.g., Kim Shayo Buchanan, *When Is HIV a Crime? Sexuality, Gender and Consent*, 99 MINN. L. REV. 1231 (2014).

233 Lash, *supra* note 116.
external requirements, or yet more loss of trust in the beneficent motives and results of science—or both. We need further study and thought on the details of the idea. We can examine precedents, such as requirements for medical professionals to report their patients for abuse and colleagues for practicing while impaired. Academic honor codes provide other useful precedents. The National Academies, or some similar group, should convene a committee to study the feasibility of such a reporting requirement and, within a short time, report with recommendations on whether and how to make it happen.

C. Express—and Feel—Humility

The He affair fed public concerns about mad, bad, and rogue scientists. Whether or not one ultimately concludes that He Jiankui violated Chinese laws, criminal or otherwise, he was a rogue scientist. He proceeded secretly, and without public discussion, to do something that he knew, or should have known, would be widely condemned. He allegedly was committing fraud to do so, at least according to official reports from Chinese authorities. He’s actions led many in the public to worry that scientists were pursuing their schemes with no regard for the law or for the opinions of their fellow citizens, citizens who were largely footing their bills. Science needs to make clear that it cannot, will not, and does not want to pursue research that is not acceptable to its society.

Before the He affair, scientists’ statements about human genome editing openly acknowledged the importance of public opinion. The Mar. 2015 article in SCIENCE, many of whose authors became members of the organizing committees of the International Human Genome Editing Summits, said we should:

Strongly discourage, even in those countries with lax jurisdictions where it might be permitted, any attempts at germline genome modification for clinical application in humans, while societal, environmental, and ethical implications of such activity are discussed among scientific and governmental organizations…

The Summary Statement of the Organizing Committee for the first Summit, in Dec. 2015, said

It would be irresponsible to proceed with any clinical use of germline editing unless and until (i) the relevant safety and efficacy issues have been resolved, based on appropriate understanding and balancing of risks, potential benefits, and alternatives, and (ii) there is broad societal consensus about the appropriateness of the proposed application.

The report issued on Valentine’s Day, 2017 by the U.S. National Academies of Science and Medicine said: ‘With respect to heritable germline editing, broad participation and input by the public and ongoing reassessment of both health and societal benefits and risks are particularly critical conditions for approval of clinical trials.’

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234 Baltimore et al., supra note 49.
235 On Human Gene Editing: International Summit Statement, National Academies (Dec. 3, 2015), http://www8.nationalacademies.org/onpinews/newsitem.aspx?RecordID=12032015a (accessed Mar. 15, 2019).
236 National Academies, supra note 51.
The U.K.’s Nuffield Council on Bioethics issued a report in July 2018 that said:

We recommend that before any move is made to amend UK legislation to permit heritable genome editing interventions, there should be sufficient opportunity for broad and inclusive societal debate.237

What all of these findings have in common is the need for public buy-in—at least acceptance if not full approval or consensus—before proceeding with human germline genome editing. At the Hong Kong Summit where He revealed his work, David Baltimore, chair of the organizing committee, initially struck the right note. Immediately after He’s appearance, Baltimore said, forthrightly, ‘There has been a failure of self-regulation by the scientific community because of a lack of transparency’.238 And, indeed, the closing statement of the organizing committee reiterated Baltimore’s condemnation of He’s work.239

But there were disturbing off-notes, both in the closing statement and in individual statements from prominent scientists. The closing statement said:

The organizing committee concludes that the scientific understanding and technical requirements for clinical practice remain too uncertain and the risks too great to permit clinical trials of germline editing at this time. Progress over the last three years and the discussions at the current summit, however, suggest that it is time to define a rigorous, responsible translational pathway toward such trials...

A translational pathway to germline editing will require adhering to widely accepted standards for clinical research, including criteria articulated in genome editing guidance documents published in the last three years.

Such a pathway will require establishing standards for preclinical evidence and accuracy of gene modification, assessment of competency for practitioners of clinical trials, enforceable standards of professional behavior, and strong partnerships with patients and patient advocacy groups.

The closing statement called for ‘continued international discussion of potential benefits, risks, and oversight of this rapidly advancing technology’. That’s fine. It did not, however, say that a ‘broad societal consensus’ would be necessary before starting clinical trials. And it did not say that, before such trials start, ‘there should be sufficient opportunity for broad and inclusive societal debate’. This closing statement could easily be read as: ‘There are a lot of technical things scientists need to figure out before this can be done. The public should have a chance to comment, but they will not make the decisions. We will’.

This impression was abetted by unfortunate statements alluding to the inevitability of human germline editing. For example, George Daley, a member of the organizing committee, one of the major speakers, Dean of Harvard Medical School, and someone I like and respect, said at the Summit:

I want to suggest that I do think it’s time to move forward from the prospects of ethical permissibility to start outlining what an actual pathway for clinical translation look like.

237 Nuffield Council on Bioethics, supra note 53.
238 Session 3, supra note 81.
239 On Human Genome Editing II, supra note 89.
What would be the regulatory standards that a group would be held to in order to bring this technology forward?

Daley’s regulatory standards did not include a societal consensus, or even social acceptance. He took a few bows toward society, but one could quite easily hear in his comments that scientists should be the ones to figure out when, and how, this new technology will be used. SCIENCE subsequently quoted Daley as saying, ‘We have to aspire to some kind of a universal agreement amongst scientists and clinicians about what’s permissible … Those who violate those international norms are held out in stark relief’. 240

This quotation does not invite the public to contribute to this ‘universal’ agreement. My complaint is not that the Organizing Committee or Daley said something wrong, but that they didn’t say something both right and important. They did not say, let alone trumpet, the crucial need for public acceptance before anyone should use genome editing technology to make babies. At a time when rogue scientists, or Science itself, is being blamed for ignoring the public, its high and mighty representatives should expressly say the following: ‘Science is part of society. The decision to use this technology belongs in part to scientists, but ultimately to societies’. That, of course, is a truisim. If a country makes the use of genomic editing technology illegal—as many have, including (effectively) the United States—then work cannot proceed there. But the He affair marked an especially important time for Science to say this, openly and clearly. The primacy of public acceptance should have been the first sentence of any reaction by scientific leaders to He’s work. Instead, it was largely absent. And this, I fear, was a self-inflicted wound.

Personally, I think that the case for germline editing if even proven safe, is strong in a few (very few) applications, and weak (but not trivial) in some others. 241 But demanding social acceptance before using it to make babies is both legally and politically right. And Science would benefit if its spokesmen made it crystal-clear that they accept—and in fact agree with—that demand. Science cannot exist, let alone thrive, without the continuing financial, legal, and political support of the societies in which it works. Its leaders need to say so: early, often, and loudly.

4. What Has Science Done So Far?

Not much. The presidents of the U.S. NAS and NAM and the Chinese Academy of Sciences published an editorial in SCIENCE on Dec. 14, 2018, calling for several actions. 242 One is increasingly detailed and concrete delineation of what conditions would need to be met to allow ethical human germline genome editing (a moratorium of a sort);
another is a mechanism for scientists to report unethical research. Exactly one day after my “final” revisions on this piece, about five and a half months after the revelation of the He experiment and five months after that editorial was published, the various academies did establish a commission to “develop a framework for scientists, clinicians, and regulatory authorities on the appropriate use of human germline genome editing.”

On the same day as the publication of the *Science* editorial, the WHO announced that it going to establish a ‘global multi-disciplinary expert panel to examine the scientific, ethical, social and legal challenges associated with human genome editing (both somatic and germ cell)’. On Feb. 14, 2019, the WHO announced the 18 panel members, drawn from many countries and co-chaired by Justice Edwin Cameron of the Republic of South Africa and former Commissioner of FDA, Dr. Margaret Hamburg. Some of the members are well known to me and I strongly endorse their selection. Others are unknown to me; one or two I know, but find them to be surprising selections.

On Mar. 13, 2019, a group of leading scientists, including many early CRISPR pioneers, released a statement in *Nature* calling for a formal ‘moratorium’ on human germline gene editing. Although they do not have formal leadership positions in *Science*, they include some very important and well respected scientists, such as Paul Berg, Nobel Prize winner and one of the parents of the Asilomar meeting on recombinant DNA; Emmanuelle Charpentier and Feng Zheng, two of the people viewed as among the most important inventors of CRISPR; Eric Lander, the director of the scientifically powerful Broad Institute, a joint venture of Harvard and the Massachusetts Institute of Technology; and 14 others.

In the same issue of *Nature*, the Presidents of three of the four groups that sponsored the International Genome Editing Summit in Hong Kong (the U.S. National Academies of Medicine and of Science and the U.K.’s Royal Society) published a response, which stated that they shared the concerns of Berg’s group and discussed what the Academies were doing. The Presidents’ response did not, however, endorse the call for a moratorium. In another letter in the same issue, NIH Director Francis Collins and Carrie Wolinetz, head of the NIH Science Policy office, express their strong support for the Berg group’s call for a moratorium.

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243 *Human Genome Editing*, World Health Organization (Dec. 14, 2018), https://www.who.int/ethics/topics/human-genome-editing/en/ (accessed Mar. 13, 2019).

244 *WHO expert advisory committee on Developing global standards for governance and oversight of Human Genome editing*, World Health Organization, https://www.who.int/ethics/topics/human-genome-editing/committee-members/en/ (accessed Mar. 13, 2019); *WHO Panel Announced GenomeWeb* (Feb. 13, 2019), https://www.genomeweb.com/scan/who-panel-announced#.XIXc4FNkWo (accessed Mar. 13, 2019).

245 Eric S. Lander, Françoise Baylis, Feng Zheng, Emmanuelle Charpentier, Paul Berg, Catherine Bourgain, Bärbel Friedrich, J. Keith Joung, Jinsong Li, David Liu, Luigi Naldini, Jing-Bao Nie, Renzong Qiu, Bettina Schoene-Seifer, Feng Shao, Sharon Terry, Wensheng Wei, and Ernst-Ludwig Winnacker, *Adopt a moratorium on heritable genome editing*, 567 *Nature* 165, 168 (Mar. 13, 2019), https://www.nature.com/articles/d41586-019-00726-5 (accessed Mar. 15, 2019).

246 Victor J. Dzau, Marcia McNutt, and Venki Ramakrishnan, *Academies’ Action on Germline Editing*, 576 *Nature* 175 (Mar. 14, 2019), https://www.nature.com/magazine-assets/d41586-019-00813-7/d41586-019-00813-7.pdf (accessed May 19, 2019).

247 Carrie D. Wolinetz and Francis Collins, *NIH Pro Germline Editing Moratorium*, 576 *Nature* 175 (Mar. 14, 2019), https://www.nature.com/magazine-assets/d41586-019-00813-7/d41586-019-00813-7.pdf (accessed May 19, 2019).
Usually, I would view this kind of dispute as an unhelpful kind of symbolic politics. A ‘moratorium’ is defined as a ‘temporary prohibition of an activity’. (As the statement itself notes, ‘By ‘global moratorium’, we do not mean a permanent ban’.) Likewise, earlier statements said germline editing of babies should not then be done—in effect, a moratorium. Indeed, most countries where this work could easily be done prohibit it, with bans that are not expressly temporary. When the work is already illegal in the U.K., the U.S., most of Europe, and (now) China, what does a call for a moratorium add?

The statement threads the needle, in a way. Its authors seek an ‘international framework’, rather than a ‘purely regulatory approach’ or an ‘international treaty’. The authors seem to recognize, at least implicitly, that a binding enforceable international agreement would be highly uncertain even after years of work. An ‘international framework’, meanwhile, could be supported by a coordinating body under an existing organization like WHO, which coordinating body would ‘convene ongoing discussions and specific consultation once a nation announces publicly that it is considering permitting a particular application’ of human germline genome editing.

To me, some of the calls for a moratorium are at least partially political theater. ‘We oppose this more than you do; you resist using the word ‘moratorium’ so we will insist you use it so that we can win’. I don’t often like political theater. I prefer my politics and policies to be substantive.

But these moves, especially by the NATURE authors, are also, in part, efforts by those who think Science has not been clear enough about heeding public acceptance to regain public trust. The authors of the NATURE statement make a clear statement on the need for societal consensus: ‘clinical germline editing should not proceed for any application without broad societal consensus on the appropriateness of altering a fundamental aspect of humanity for a particular purpose. Unless a wide range of voices are equitably engaged from the outset, efforts will lack legitimacy and might backfire’. I understand and agree with the impulse for broader societal consensus; I just don’t see the importance of the ‘M’ word, except perhaps as a good tactical attempt at regaining public trust.

Six days after the NATURE comment was published, and about a month after WHO announced the membership of its panel, the panel took its first action. The Advisory Committee on Developing Global Standards for Governance and Oversight of Human Genome Editing, as it was now called, announced at the end of its first meeting on May 19 that it had recommended WHO to create a registry covering all studies of clinical applications for both somatic cell and germline genome editing. It called for the registry to be transparent (and presumably public). The report on the meeting said a failure to register relevant research should be considered ‘a fundamental violation of responsible research’. It urged that scientific publishers and funders of research require

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248 Advisory Committee on Developing Global Standards for Governance and Oversight of Human Genome Editing, Report of the First Meeting (May 19, 2019), https://www.who.int/ethics/topics/human-genome-editing/GenomeEditing-FirstMeetingReport-FINAL.pdf?ua=1 (accessed May 19, 2019); see also Jon Cohen, WHO Panel Proposes New Global Registry for all CRISPR Human Experiments, Science (Mar. 29, 2019), https://www.sciencemag.org/news/2019/03/who-panel-proposes-new-global-registry-all-crispr-human-experiments (accessed Apr. 2, 2019).
participation. (SCIENCE, CELL, and NATURE indicated at least general support for the idea.249) The Committee is establishing a working group to design the registry in all its details.

The meeting report said the Committee ‘agreed with the views previously expressed that ‘it would be irresponsible at this time for anyone to proceed with clinical applications of human germline genome editing’. In the virtual press conference after the meeting, Dr. Hamburg, the co-chair, answered a question about a moratorium by saying:

Certainly the issue of whether a moratorium might have a role to play will be part of those discussions, but what we are really trying to do is look at the broader picture and look at how there can be a framework for responsible stewardship. I don’t think that a vague moratorium is the answer to what needs to be done.250

As far as I can tell, the WHO has not acted yet on the May recommendations from the Committee, although that may be because the Committee’s working group is working on the details of the registry. The Committee was asked to deliver its final report to the WHO Director General within 18 months.

The proposed registry seems to me a first step, though the details (particularly around of information mandatory information disclosure, to which researchers, or companies, might be strongly opposed) may prove sticky. But it is just a start. At some point the Committee may urge the kind of actions I think are needed. It has not done so yet. I wish the Committee good luck; they will surely need it: WHO is a notoriously bureaucratic and political organization.

For a long time, nothing much had been heard about the efforts of the two U.S. Academies and the Royal Society. The March letter to NATURE stated that the three organizations

are leading an international commission to detail the scientific and ethical issues that must be considered, and to define specific criteria and standards for evaluating whether proposed clinical trials or applications that involve germline editing should be permitted. Dozens of scientific academies around the world are lending their support to the commission.251

As noted above, on the day after my final submission of this article, the Academies announced the creation of an International Commission on the Clinical Use of Human Germline Genome Editing and its membership.252 In the following five weeks, through the revision of the proofs of this article, it does not seem to have taken any action.

249 Sara Reardon, World Health Organization Panel Weights in on CRISPR-Babies Debate, 567 Nature 444-445 (May 19, 2019) https://www.nature.com/articles/d41586-019-00942-z (accessed May 19, 2019).
250 WHO, WHO-RUSH Human Genome Editing 1st Meeting VPC (Mar. 2019), https://www.who.int/ethics/topics/human-genome-editing/Human-genome-editing-1st-advisory-committee-VPC.pdf?ua=1 (accessed May 19, 2019).
251 Dzau et al., supra note. 245.
252 https://www8.nationalacademies.org/pa/projectview.aspx?key=51725 (creation) and http://www.nationalacademies.org/gene-editing/international-commission/commission-members/index.htm?ga=2.214477074.468638605.1561837860-1221268517.1561837860 (membership), both last accessed on June 29, 2019.
The call for a moratorium in *Nature*, the response from the Academies, the WHO Committee report—all sought an undefined, perhaps undefinable, social consensus. Beyond that, as far as I can tell, Science has done nothing toward enforcing deterrence, creating disclosure, or expressing humility. It should.

**B. China Should (Continue to) Strengthen Its Research Regulatory System**

It is not a shock that the He experiment took place in China. China has poured vast sums into biological, and particularly genetic, research in the past two decades, and this investment has paid off. It is now clearly one of the two or three most important countries in the world for genetics research, still behind the United States, but challenging (or perhaps surpassing) the United Kingdom. With the funding has come a ‘wild west’ atmosphere, where Chinese scientists talk about deeply understanding the genetic roots of human intelligence and blithely use CRISPR to miniaturize pigs; to add longer hair and more meat to domestic goats; to add muscle to beagles; to modify the DNA of monkeys and of human embryos; and, ultimately and allegedly, to edit the germline genome of human babies. And they do so with pride in the great advances of Chinese science, with a nationalism that seems to me quite similar to that of the United States.

Some voices in the West want to pick fights with China, for various reasons. There’s nothing like a dangerous and worrisome international rival to spark increased domestic interest and funding. But one of the arguments advanced, more or less subtly, is an ultimately racist one that the Chinese have no ethics—they are ‘the Yellow Peril’, unassimilable, incomprehensible, inevitably ‘the other’.

As a Californian, I am painfully aware of how my state—and indeed, the founders of Stanford University, my employer and undergraduate school—used and abused imported Chinese laborers. And then California (though not the Stanfords), in a burst of populist racism, turned against them. Californians lobbied successfully for a ban on Chinese immigration to the United States in the 1875 Page Act, banning immigration of Chinese women, and the 1882 Chinese Exclusion Act, banning immigration of Chinese laborers. In addition to federal law, California and its counties and cities adopted further stringent and onerous restrictions on the Chinese who were already in the state.

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253 Ed Yong, *Chinese project probes the genetics of genius*, *Nature News* (May 14, 2013), https://www.nature.com/news/chinese-project-probes-the-genetics-of-genius-1.12985 (accessed Mar. 13, 2019).

254 David Cyranoski, *Gene-edited ‘micropigs’ to be sold as pets at Chinese institute*, *Nature News* (Sep. 29, 2015), https://www.nature.com/news/gene-edited-micropigs-to-be-sold-as-pets-at-chinese-institute-1.18448 (accessed Mar. 13, 2019).

255 Sarah Zhang, *Would You Buy a Genetically-Engineered Cashmere Sweater?*, *The Atlantic* (Oct. 26, 2016), https://www.theatlantic.com/health/archive/2016/10/cashmere-goat-crispr/505163/ (accessed Mar. 13, 2019).

256 Antonio Regalado, *First Gene-Edited Dogs Reported in China*, *MIT Technology Review* (Oct. 19, 2015), https://www.technologyreview.com/s/542616/first-gene-edited-dogs-reported-in-china/ (accessed Mar. 13, 2019).

257 Helen Shen, *First monkeys with customized mutations born*, *Nature News* (Jan. 30, 2014), https://www.nature.com/news/first-monkeys-with-customized-mutations-born-1.14611 (accessed Mar. 13, 2019).

258 Megan Molteni, *With Embryo Base Editing, China Gets Another CRISPR First*, * Wired* (Aug. 21, 2018) https://www.wired.com/story/crispr-base-editing-first-china/ (accessed Mar. 13, 2019).

259 Mark E. Steiner, *Inclusion and Exclusion in American Legal History*, 23 *Asian Am. L. J.* 69 (2016).
America, as immigrants or as native-born citizens.\textsuperscript{260} To me, this is a shameful memory.

But it seems more than just a memory, as I see people decrying the lack of ethics by the Chinese. On some points, the Chinese government may, of course, act unethically (as may all governments). More pertinent to this discussion: China’s treatment of HIV-positive people is deeply disturbing.\textsuperscript{261} But, when it comes to research ethics, as far as I can tell the Chinese government and research establishment has roughly the same sets of rules as the rest of the developed world, including (for the most part) the United States. China is not as concerned about research with human embryos as the United States and some other western countries are; neither are they as sentimentally concerned about genetic modifications to animals that do not clearly implicate the modified animals’ welfare. But, for human subjects research, informed consent, and for both human and most non-human research, some advance weighing of the risks to the research subjects against the possible benefits exist in China as well.

What has been different is how research is implemented on the ground. Some of the Chinese reports, particularly the Xinhua report of the Guangdong investigation, have cast He Jiankui as an impossible-to-stop ‘lone wolf’. But I think the real problem is that China did not have the depth of regulations and regulatory bodies—and regulatory mindset—necessary to stop him. The United States has a big, bureaucratic, and often annoying set of structures for controlling most research, from Institutional Review Boards, Institutional Animal Care and Use Committees, Biosafety Committees, and Embryonic Stem Cell Research Oversight Committees, often managed by research oversight departments in universities, research institutes, and pharmaceutical and biotech companies. These local committees oversee compliance, but they also report to the federal government, which ultimately wields the power to bar federal funding at non-compliant institutions, a power those entities must take seriously.

This is not a streamlined, efficient, and easy system. Scientists often bridle at the delays they go through to cross every ‘i’ and dot every ‘t’ in their human subjects or animal use protocols. But they do constrain behavior.

China comes from a very different tradition. Although imperial China may have been the world’s longest surviving bureaucracy (only the Catholic Church gives it a run for its money), the Communist Revolution produced an interregnum. For roughly 30 years between the 1949 victory of the revolution and the rise to power in 1979 of Deng Xiaoping, China was, in effect, a lawless land. It was not a place without authority—as far too many people found out to their death and dismay—but it operated through ad hoc decisions by the Communist Party and its leadership, not by legislative statutes implemented transparently and evenhandedly by bureaucracies.

For the last 40 years, China has been trying to ‘legalize’ itself, passing statutes and creating bodies to implement them. This is particularly hard in a country roughly the geographical area of the United States, Brazil, Canada, or Australia, but with a population

\textsuperscript{260} Leigh Bristol-Kagan, \textit{Chinese Migration to California, 1851−1882: Selected Industries of Work, the Chinese Institutions and the Legislative Exclusion of a Temporary Work Force}, PhD diss. (Harvard University, Cambridge, MA: 1982).

\textsuperscript{261} Frankie Huang, \textit{Letter: How China’s Penchant for Eugenics Led to CRISPR Babies}, CAIXIN GLOBAL (Dec. 17, 2018), \url{https://www.caixinglobal.com/2018-12-17/letter-how-chinas-penchant-for-eugenics-led-to-crispr-babies-101360013.html} (accessed Mar. 15, 2019).
The He Jiankui affair

...roughly four times, six times, thirty times, and fifty-five times as large. It is not at the stage of a developed western society, and may never be, but it is moving in that direction. But it moves fitfully. Control over threats to the power of the Communist Party are carefully watched and thoroughly handled. Control over biomedical research—not so much.

China had and has requirements for approval of human subjects by local committees. It had and has regulations concerning ethical and unethical genome research. But, prior to the He affair, it did not have powerful structures to implement those aspirations, or the precedent of taking action against rogue scientists. I am writing the final revisions of this almost six months after the revelation of He’s experiments. Science has scarcely acted, but China has, several important ways.

First, it took some rapid actions in response to the He revelations. Almost immediately after the announcement of He’s work in late November, it froze all funding for his research.262 And, in December, the Chinese Education Ministry ‘sent notices to universities requiring self-checks on research related to gene editing’, telling the ASSOCIATED PRESS by email that ‘it called on educational institutions to strengthen management of scientific research ethics and inspect research involving gene-editing technology’.263

Then, in January, China’s government announced its view that He’s work was illegal as violating a more than 15-year-old regulation banning unethical or immoral human genome research.264 The regulation is vague and, to an American lawyer’s eyes, would not clearly apply to He’s work, but legal systems differ. Presumably, any actions against He will go through some kind of judicial or administrative process, but I suspect the Party’s interpretation of the regulation will stand. That should, in itself, deter this kind of research in one of the world’s three leading genomics countries and one that is home of about 15% of humanity.

Later in January, China’s President, Xi Jinping, called for tighter regulation of gene editing through new legislation.265 On Feb. 27, China announced new regulations on ‘high risk’ technologies, including gene editing, which would be governed by a committee of China’s cabinet, the State Council.266 In early March, STAT’s Qiu reported that China had decided to set up

a powerful new national medical ethics committee, which will approve all clinical trials involving high-risk biomedical technologies, is at the center of a regulatory shakeup Chinese authorities are planning in the aftermath of the widely condemned ‘CRISPR babies’ experiment....

262 Sui-Lee Wei, China Halts Work by Scientist Who Said He Edited Babies’ Genes, The N.Y. Times, (Nov. 29, 2018), https://www.nytimes.com/2018/11/29/science/gene-editing-babies-china.html (accessed Apr. 4, 2019); Research Activities of Persons Halted Over Gene-Edited Babies Incident, Xinhua (Nov. 29, 2018), http://www.xinhuanet.com/english/2018-11/29/c_137640174.htm (accessed Apr. 4, 2019).
263 Yanan Wang and Fu Ting, China drafts rules on biotech after gene-editing scandal, ASSOCIATED PRESS (Feb. 27, 2019), https://www.apnews.com/47aa8f8a382c4ae19e6ce202f93dd8 (accessed Mar. 12, 2019).
264 Serenitie Wang, Chinese authorities say world’s first gene-edited babies were illegal, CNN (Jan. 21, 2019), https://www.cnn.com/2019/01/21/health/china-gene-editing-babies-intl/index.html (accessed Mar. 15, 2019).
265 Tom Hancock and Wang Xueqiao, China set to tighten regulations on gene-editing research, FIN. TIMES (Jan. 25, 2019), https://www.ft.com/content/a464bd9c-f869-11e8-af46-2022a0b02a6c (accessed Mar. 12, 2019).
266 Wang and Ting, supra note 262.
The technologies that will be regulated by the ethics committee are often new and are deemed risky either because of safety or moral concerns. They will include not only gene editing, but also cloning, cell therapy, xenotransplantation, mitochondrial replacement, and nanotechnology.\footnote{Jane Qiu, China creating national medical ethics committee to oversee high-risk clinical trials, STAT (Mar. 5, 2019), \url{https://www.statnews.com/2019/03/05/china-creating-national-medical-ethics-committee/} (accessed Mar. 12, 2019).}

With a planned 30-member staff, the national ethics committee—personally approved by President Xi Jinping—will report to the State Council, China’s cabinet, and have regulatory jurisdiction over nearly a dozen ministry-level agencies that fund or regulate medical research and applications.

Qiu quotes David Archard, chair of the U.K.’s Nuffield Council, and Wisconsin law professor Alta Charo (co-chair of the 2017 National Academies report) as pointing out successes with national oversight committees, but noting the importance of inspection powers, which are not clearly present in this proposal:

What’s lacking, said both Archard and Charo, is an inspection body that would work in conjunction with the national ethics committee. In both the U.S. and the U.K., inspections—often in the form of surprise visits—is \textit{sic} a critical aspect of regulatory oversight. ‘It has turned out to be incredibly important because the reports that are delivered [to federal agencies] are often not quite correct or not quite complete’, said Charo. ‘It’s very important for Beijing to know what’s going on at the local level’.

And on May 20, 2019, China announced that the latest draft of its revised Civil Code would include ‘human genes and embryos in a section on personality rights to be protected. Experiments on genes in adults or embryos that endanger human health or violate ethical norms can accordingly be seen as a violation of a person’s fundamental rights’.\footnote{David Cyranoski, China Set To Introduce Gene-Editing Regulation Following CRISPR-Baby Furore, Nature (May 20, 2019), \url{https://www.nature.com/articles/d41586-019-01580-1} (accessed May 21, 2019).} This version of the revised Civil Code, which has been undergoing revisions since 2002, is expected to be adopted in Mar. 2020; the human genome provisions are a late addition.

It is not just Westerners who are calling for more action by China. Recall that 122 Chinese scientists and ethicists signed a letter decrying the He experiment, which was disseminated on WeChat less than 24 hours after the story broke. More recently, on May 8, 2019, four Chinese ethicists and researchers, Ruipeng Lei, Xiaomei Zhai, Wei Zhu, Renzong Qiu, called in \textit{Nature} for a ‘reboot’ of ethics governance in China.\footnote{Ruipeng Lei, Xiaomei Zhai, Wei Zhu, Renzong Qiu, Reboot Ethics Governance in China, 569 Nature 184, 186 (May 8, 2019), \url{https://www.nature.com/articles/d41586-019-01408-y} (accessed May 19, 2019).} They provide six specific recommendations, summarized as regulate, register, monitor, inform, educate, and end discrimination. They also call for a much larger and more transparent international investigation into the He affair than the preliminary investigation by Guangdong province, the details of which, itself, have only been made public.

\footnote{267 Jane Qiu, China creating national medical ethics committee to oversee high-risk clinical trials, STAT (Mar. 5, 2019), \url{https://www.statnews.com/2019/03/05/china-creating-national-medical-ethics-committee/} (accessed Mar. 12, 2019).\footnote{268 David Cyranoski, China Set To Introduce Gene-Editing Regulation Following CRISPR-Baby Furore, Nature (May 20, 2019), \url{https://www.nature.com/articles/d41586-019-01580-1} (accessed May 21, 2019).\footnote{269 Ruipeng Lei, Xiaomei Zhai, Wei Zhu, Renzong Qiu, Reboot Ethics Governance in China, 569 Nature 184, 186 (May 8, 2019), \url{https://www.nature.com/articles/d41586-019-01408-y} (accessed May 19, 2019).}}
only through a short article from the national press agency. According to interview with Dr. Qiu, ‘Nothing suggests another investigation is underway’. 270

The NATURE article ends with this reminder, and hope:

It has been only around 30 years since bioethics was established in China. And it is worth remembering that unethical research practices were rise in the West in the early days of ethics governance. Take the infamous Tuskegee study, in which the US Public Health Service tracked — but did not treat — 399 black men with syphilis from 1932 to 1972. Just as the revelation of that research prompted the 1978 Belmont Report, which protects human participants in studies or clinical trials, the ‘CRISPR babies’ scandal must catalyse an overhaul of science and ethics governance in China. 271

When I began writing this article, this section was going to call on China to act quickly to bring this research under greater regulatory control. China largely has beaten me to it; I can only call for China to be serious and diligent in implementing its proposals, and the extensions suggested in the bioethicists’ article. And for us all to have a moment of deeply ambivalent reflection on the ability of some governments to move quickly while other governments seem to be unable to move at all.

CONCLUSION

He Jiankui has taken us on a long and winding path. His production of those two babies was, in my view, unforgivably reckless. He deserves our condemnation. But I want to close by bringing us back to the near future—and to human germline genome editing. I have, I think justly and comprehensively, condemned He’s experiment, but have done so without focusing particularly on the merits or demerits of human germline genome editing. This article is already too long; that broad and general topic will be the subject of another piece. But I will say that, over the next few decades, I do not think human germline genome editing is likely to be very important. (Beyond 40 or 50 years, I have no clue.) Its safety, in several respects, is uncertain, and it has few potential benefits—particularly when compared with other, more conventional interventions, such as embryo selection. On the other hand, I think it has few distinct problems, practical or deeply ethical (one might even say ‘philosophical’). It is new, it is interesting (at least, if you have read this far, I have to assume you find it—or found it—interesting), and it does present some immediate issues, including some that demand immediate action.

But, like Dolly’s birth, He Jiankui’s CRISPR’d babies are not the end of the world—or the beginning of the end of our species. They are a challenge both to the ability of Science to regulate itself, and to the world’s trust in Science. Drastic action is not needed but, in its aftermath, useful things should be done. And, just as important, useful things must be said.

270 See also the email interview with Dr. Qiu in Jon Cohen, Chinese Bioethicists Call for ‘Reboot’ of Biomedical Regulation After Country’s Gene-Edited Baby Scandal, SCIENCE, https://www.sciencemag.org/news/2019/05/chinese-bioethicists-call-reboot-biomedical-regulation-after-country-s-gene-edited-baby (accessed May 19, 2019).
271 Lei et al., supra note 268, at 186.