MEDICINE AND SOCIETY

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The Future of Gene Editing — Toward Scientific and Social Consensus

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On the day after Thanksgiving 2018, Jennifer Doudna, a biochemist at the University of California, Berkeley, whose research on bacterial immune systems led to the gene-editing technique known as CRISPR (for Clustered Regularly Interspaced Short Palindromic Repeats),[1] received a startling email from the Chinese scientist He Jiankui. "Babies born," read the subject line. Though Doudna was previously unaware that He had been working to create the world's first "CRISPR babies," she had long worried that CRISPR-related research was leaping ahead of the consensus necessary to support its ethical use. In her memoir about gene editing,[2] Doudna describes a nightmare in which she is summoned by a pig-faced Hitler to describe the potential implications of the "amazing technology" she developed. But it's the preoccupation of Doudna's waking life, "that through a series of reckless, poorly conceived experiments, scientists would prematurely implement CRISPR without proper oversight or consideration of the risks," that has proven more prescient.

Indeed, as the details of He's experiment emerged, it quickly became impossible to separate the implications of the science from the ethics violations that had enabled it. He apparently attempted to edit the *CCR5* gene in the germlines of two embryos. *CCR5* is thought to be the major receptor through which HIV gains access to T cells, and He aimed to confer lifetime resistance to HIV. The magnitude of negligence was staggering — from the absence of clinical need (there are safe and effective ways to prevent HIV), to the uncertainty of harms (the twins may be at heightened risk from infections such as West Nile virus and influenza, and other potential consequences of both on- and off-target effects remain unknown), to a misleading consent process (the experiment was described as an "AIDS vaccine development project"), to a total lack of transparency (the data have not yet been published).[3]

Though some observers questioned whether the babies were even real, Kiran Musunuru, a cardiologist and geneticist at the University of Pennsylvania who reviewed He's data for the Associated Press, believes that the data are real precisely because they are so flawed. Musunuru explained that He had sampled only three to five cells out of the hundreds in each blastocyst-stage embryo. Even though cells from both embryos clearly showed mosaicism, He proceeded with implantation. "If He were faking it," Musunuru said, "it would be truly bizarre for him to include data showing a strong sign of a problem." Emphasizing that preclinical data have clearly shown significant risks related to mosaicism, Musunuru described the most fundamental ethical breach: exposing the embryos to all the risks and none of the benefits of gene editing.

The condemnation from the scientific community was swift — as was the realization that such rogue behavior was probably inevitable. Shortly after the news broke, Derek Lowe, a medicinal chemist, wrote in his blog that "Everyone has been standing around looking at this weapon; He Jiankui is just the guy who walked up and pulled the trigger before anyone was quite clear where the thing was aimed."[4] Given that expert groups, including one convened by the National Academy of Sciences (NAS), have outlined principles to guide ethical and safe gene-editing research,[5] He's behavior has forced a reckoning within the scientific community, leading many observers to call for an international consensus to explicitly detail the circumstances under which clinical translation should

be permitted.[6] As Doudna remarks, however, perhaps the silver lining of this moment is that we have been pushed to confront, publicly, globally, and rather urgently, some of the thorny issues raised by germline-editing research.

AN ETHICAL FRAMEWORK

The ethics of the procedure can be considered only within the context of potential clinical applications, and many ethicists propose a three-category framework: enhancement, medical benefit, and unmet medical need. Enhancement refers to fostering desirable traits such as greater height and intelligence. Though it's viewed as the least ethical of the three potential applications (and the NAS recommends against it),[5] when one considers specific examples, the ethics become less clear-cut. For example, although the NAS notes that it seems unacceptable for prospective parents to use gene editing to increase their children's muscle strength to enhance future athletic prowess, if the same technique could confer normalcy to a child with muscular dystrophy, would such use be ethically sound? Matt Porteus, a Stanford geneticist who served on the NAS committee, believes that enhancement should only ever be considered as a means to restore normalcy. In taking otherwise healthy embryos and attempting to confer a trait not otherwise prevalent in the population, He's project was clearly the opposite of this.

Medical benefit, for which potential indications are myriad, could entail reduction in the risks for common, complex diseases such as Alzheimer's disease, breast cancer, or heart disease. But it is also difficult to make an ethical case for germline editing for these purposes, given the unknown risks. Moreover, researchers are investigating the potential use of somatic-cell gene editing, which targets only the specific organs involved and only in adults or children, for the same purpose. Another conceivable indication in this category, described to me by Michelle Meyer, a professor of bioethics at Geisinger, is the conferral of resistance to an infectious disease that is endemic and fatal and for which neither vaccines nor treatments exist. The fact that evolution played a similar role in selecting for sickle cell trait in malaria-endemic regions highlights both the merits of this potential use and the challenge of anticipating unintended consequences. Meyer emphasizes that the benefits, such as avoiding death, need to be very substantial to offset the risks. "The He scenario did not even approach the required risk–benefit threshold," she said.

Unmet medical need applies to the very rare cases in which the only option for conceiving a healthy child would be gene editing — for instance, when both prospective parents have an autosomal recessive disease such as sickle cell anemia or when one of them has two copies of a gene for an autosomal dominant condition such as Huntington's disease. Although such cases are rare, because they present compelling examples of medical need, this tends to be the area in which there is the greatest consensus.

But even here, things become murky when one considers the practical realities of in vitro fertilization (IVF), which is required for germline editing. For instance, what if a couple seeks to conceive and one of them carries a single copy of the dominant Huntington's disease gene? Today, such couples attempting to conceive using IVF could choose to undergo preimplantation genetic diagnosis (PGD), seeking to select the roughly half of their embryos that would be disease-free. Noting that a paucity of viable embryos contributes to the high failure rate of any given IVF–PGD cycle and that a growing percentage of couples are using personalized genomics to reveal potentially heritable diseases, George Daley, the dean of Harvard Medical School and author of international guidelines on stem cell research and clinical translation, points out that for people with autosomal dominant diseases, germline editing could theoretically double the chances of conceiving. But he also urges caution: "There's an awful lot of more research, and more deliberation on the societal and ethical issues, that needs to happen before this would ever be acceptable. Otherwise there will be a huge backlash to the use of such technology."

IS CONSENSUS POSSIBLE?

Even within the scientific community, backlash is already occurring. In the wake of the He scandal, some scientists, including CRISPR pioneer Feng Zhang,[7] have called for a moratorium on implantation of edited embryos until a broader social consensus is reached.[8] But others, like science journalist Carl Zimmer, argue that "genetically modified people" are already among us.[9] Zimmer points to mitochondrial replacement therapy, approved in Britain for women with severe mitochon-

drial disease, which entails combining a healthy woman's mitochondrial DNA with a diseased woman's chromosomes to avert devastating disease in offspring. Such therapy is banned in the United States, but Zimmer tells the story of an American fertility doctor who "quietly" went to Mexico to perform the procedure in a Jordanian woman who then refused to let scientists follow the resulting child. As Jeffrey Kahn, the director of the bioethics institute at Johns Hopkins, emphasizes, "Prohibitions tend to end up with worse outcomes. They drive people to places where there are fewer or no rules." With mitochondrial replacement therapy, at least, the consequences may be higher risks for patients and a lost opportunity for science.

But a far greater concern is that existing and appropriate regulations won't be followed. (He's research, currently illegal in China, is a case in point.) Achieving social consensus will depend as much on clear communication about the ethical boundaries of the science as on reassurance that those boundaries won't be crossed. Such reassurance may not be possible. In China, the response to He's behavior has reportedly ranged widely.[10] While some commentators condemned his behavior, others focused less on the ethical breach than on the opportunity to bolster China's international reputation with a scientific milestone. Moreover, the diversity of cultural attitudes toward germline editing may render any prohibition difficult to sustain. For instance, in addition to heightened stigma associated with disability and infertility,[11] another enduring effect of China's one-child (now two-child) policy is intense pressure to have healthy and smart children.

Indeed as Julian Savulescu, a professor of practical ethics at the University of Oxford, told me, the Chinese have spent the past decade sequencing the genomes of people with high intelligence, with the theoretical intent of eventually improving people's cognitive abilities (if only by selecting embryos with the most potential). Savulescu, who called He's behavior monstrous, nevertheless sees a potential future role for gene editing in providing opportunities for happier, healthier lives. "Disease is just a statistical definition," Savulescu said. He explained that, for example, intellectual disability, defined by an IQ below 70, affects a substantial proportion of the population. If we had the technology to enhance cognitive ability, he wondered, would it be fair to let people with intellectual disability suffer? Savulescu, who thinks we will be forced to answer such questions within the next decade, notes that the major objection to such enhancement is that it would exacerbate inequality. Avoiding a two-tiered society, Savulescu argues, requires creation of a public health system in which gene editing, when it is safe, is available to everyone, or at least to those in greatest need.

Others are far more circumspect. Recent data, such as those from a genomewide association study revealing an association between a particular polygenic risk score and educational attainment,[12] highlight the potential of predictive genomic modeling. But that doesn't mean "CRISPR-ing" babies for these favorable traits will ever be beneficial. One limitation is environmental variability: favorable traits in one setting may be harmful in another. Cecile Janssens, a professor of epidemiology at Emory, draws an analogy to car design: a convertible might be ideal for a summer evening, but deadly on a mountain pass.[13] For other experts, the issue is one of more basic biology. With a trait like intelligence, which is influenced by so many genes, you can't achieve enhancement without introducing all sorts of mutations that confer unintended harms. In short, says Musunuru, "Biology is really messy."

REAL LIVES

The most frequently mentioned risks posed by germline editing are off-target mutations that raise the specter of cancer. "There's not been a single report of an animal model in which CRISPR (unintentionally) caused cancer," according to Musunuru — but no one knows how off-target effects may manifest in humans, who live much longer than the animals that have been studied. Musunuru is most concerned about whether germline editing heightens the risk for other diseases, given that some genetic loci have opposing effects on disease susceptibility. For example, *APOE4* may both increase susceptibility to Alzheimer's disease and promote better memory function in young adults. Such variable effects have also been observed for type 1 diabetes and Crohn's disease.[14] Although clinical translation invariably requires acceptance of uncertain risks, concerns about unknown harms loom larger when those risks will be passed to future generations.

Yet as Anupam Jena, a Harvard physician and

economist, points out, there's also potential harm in quashing or delaying technology that could significantly transform people's lives. Economists frame these challenges less in terms of "doing no harm" than in terms of maximizing welfare. "That means explicitly recognizing that there is a trade-off between how fast and how safely we can help people," Jena told me. But even this reframing requires us to consider what welfare, in the context of potentially heritable diseases, really means. No parents, for instance, wish disability on their children. Yet many people who live with disability perceive their quality of life to be as high as that of people without disability.[15] In seeking public consensus regarding germline editing, how might we navigate these sorts of tensions?

As Stanford bioethicist Kelly Ormond emphasizes, research is required to elucidate the values and preferences of people whose lives would be affected most imminently by germline editing. In addition, in a society where many people's understanding of gene editing comes from dystopian movies like *Gattaca*, broad educational efforts are needed to clarify what the technology can and can't do. Meyer suggests emphasizing that, in some ways, germline editing is not a radical departure from current reproductive technology. For example, we've long exerted some control over our offspring's traits, whether by selecting mates or by choosing a gamete donor on the basis of desired qualities. As necessary as research and education may be, however, there will remain unanswerable questions.

Even if scientists could somehow guarantee that editing a particular gene would cause no catastrophic, lasting, or untreatable harm far down the line, would it be an unalloyed good to save future generations from genetic conditions? Many people with disabilities, for instance, protest efforts to use advanced reproductive technology to prevent the creation of new humans with the same disabilities: not only may disability-rights activists see their difference as inherent to their identity; they may also recognize the devaluing of their own lives that such efforts reflect and, more generally, worry about a future in which human diversity is purposely curtailed and discrimination justified by science.

So when they are eventually offered gene-editing opportunities, prospective parents may find their choices difficult. Ethan Weiss, a cardiologist and scientist at the University of California, San Francisco, is also the father of Ruthie, a 12-year-old who was born with albinism, a monogenic disease that has left her legally blind. Ruthie skis, excels on her basketball team, and is an inspiration everywhere she goes. Ruthie has said that she doesn't wish her disease had been edited away, nor does she believe she would attempt to spare her future children.[16] Yet as Weiss told me, had he and his wife used preimplantation genetic diagnosis, they would have chosen an embryo without the mutation. "That's what terrifies me," Weiss said: not just that their family would never have experienced Ruthie's magical influence, but that as a society, "We will marginalize difference even more."

But whereas some people thrive with disability, some have genetic diseases that either cause early death or are so crippling that the opportunities Ruthie has had are simply impossible. Who is qualified to decide whether it's ethical to alter those children's fate? As Doudna writes, "That we are unprepared for such colossal responsibility, I have no doubt. But we cannot avoid it."[2] We will no doubt spend decades debating whether and how to use germline editing ethically and safely. In the meantime, Weiss's sense that there's no such thing as an "informed decision" for parents who are offered such emerging technologies may be as true for life as it is for the science: "You can't know," he said, "until you know."

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