INTERVIEW

"A Viable Path Toward Responsible Use"

A discussion with Jennifer Doudna on the risks and rewards of CRISPR/Cas9 gene editing.

Jennifer Doudna, a professor of chemistry and molecular and cell biology at the University of California, Berkeley, and codiscoverer of the CRISPR/Cas9 gene-editing technology, served on the organizing committee of the Second International Summit on Human Genome Editing, held in Hong Kong in late 2018. The editor of *Issues in Science and Technology*, William Kearney, was there too, managing communications for the US National Academy of Sciences and the US National Academy of Medicine, which cohosted the summit with the Royal Society of the United Kingdom and the Academy of Sciences of Hong Kong.

The summit made global headlines when the Chinese scientist He Jiankui stunned the organizers and the world by presenting how he had used CRISPR to edit the early embryos of two recently born twin girls in what he said was an effort to prevent them from contracting HIV. A little over a year after the summit, Kearney interviewed Doudna to ask her to reflect on the dramatic events that unfolded there, and how she hopes the clinical promise of genome editing is pursued responsibly—with proper consideration by society of its ethical implications—going forward.

Our Second International Summit on Human Genome Editing was a memorable event for obvious reasons, but I have one striking memory in particular, of helping you escape a gaggle of reporters in the aftermath of He Jiankui's presentation. We snuck out a side door of the university auditorium, and you turned to me in the hallway and said, "Bill, I feel sick to my stomach." "Because this is the day you feared?" I asked. "It's exactly the day I feared," you replied. Can you recall how you were feeling and what you were thinking after just hearing He describe how he used CRISPR/Cas 9 to edit the embryonic genomes of newborn twins?

I felt stunned and sickened. I knew it was a possibility that someone might cross what we thought was a clear ethical red line by going against scientific consensus and applying CRISPR in human germline cells. What I didn't anticipate is that it would happen so soon and that we would find out about it only after the birth of the infants.

Do you feel any different about it a year later?

No, I am still shocked and disgusted by this news. The fallout for everyone concerned continues—the health and future of the children, the fate of the scientist, and the public perception of CRISPR technology. However, I am encouraged by the broad global rejection of the clinical process used in this case and by the calls for CRISPR's ethical use supported by stronger regulations and consequences that will not stifle the potential of the technology.

You recently wrote in* Science *that "although human embryo editing is relatively easy to achieve, it is difficult to do well and with responsibility for lifelong health outcomes." Do you worry that there are false assumptions that genome editing is more precise than it really is? What are the scientific and medical unknowns that need to be better addressed before ever considering embryo editing in clinical applications?

It is vital that safety concerns, including off-target effects and unexpected complications, are fully understood and resolved before these tools are widely used. I am encouraged by the careful studies currently underway in a US patient with sickle cell disease, and another with beta thalassemia. This is the sort of deliberate, medically necessary work that is aligned with current Food and Drug Administration regulations and will likely result in outcomes that are safe and effective.

The main challenge in embryo editing is not scientific—although scientific advances are still needed before this technology can be used safely—but rather ethical. What does it mean to give medical consent to a procedure that will impact not only your child but future generations? Which modifications should be considered as medical treatment, and which should be viewed as enhancements? Does eradicating a genetic condition create a stigma for those who continue to live with it? These are profound questions that require a broad public conversation.

What do you think about the notion of a moratorium on human germline editing? You haven't signed on to calls for a moratorium, although you have been a member of the summit-organizing committees that stated it would be irresponsible to proceed now.

My colleagues and I effectively called for a moratorium (although we avoided using that term) in spring 2015 in a Perspective in *Science*. And yet four years later that "moratorium" was ignored by He Jiankui and his enablers. One bad actor decided to act out of self-interest, and it may be the beginning of a wave of unethical experimentation. I believe that moratoria are no longer strong enough countermeasures, and instead stakeholders must engage in thoughtfully crafting regulations of the technology without stifling it.

There have been reports that a number of US scientists may have known, or at least were growing increasingly concerned, that He Jiankui intended to implant edited embryos to establish a pregnancy. In hindsight, do you think alarms should have been sounded earlier? Does the scientific community need new mechanisms to report concerns if scientists become aware of potentially rogue behavior in the future—even if in another country?

While I believe that it would have been preferable if alarm bells had been sounded earlier, the reality of confidential conversations in science, and the preeminence of abiding by the rules of confidentiality, put the US scientists who might have had concerns about his research in a complicated position. In my opinion, one mechanism to avoid this issue from happening again would be a whistleblower line to report concerns anonymously to an organization such as the World Health Organization. Additionally, a statement from an organization such as WHO could help clarify that nondisclosure agreements should not be considered binding in the case of severe ethical concerns.

Do you worry that the He incident was a setback for public understanding or acceptance of genome-editing technology, and of its potentially revolutionary use in treating disease?

Yes, public awareness of CRISPR's positive potential was growing steadily, but He's actions spiked concerns and dented confidence that the scientific community can deploy it safely and appropriately. We encourage public debate and want to show the public that we can apply the correct guardrails to ensure the technology delivers groundbreaking somatic treatments for millions.

What do you believe are some of the most promising potential uses of CRISPR for treating disease?

There is vast potential for CRISPR to become a standard of care for treating disease. Clinical trials using CRISPR are already underway for patients with cancer, blood disorders, and eye disease. In the next few years we may see CRISPR-derived medical breakthroughs for people suffering from liver disease, muscular dystrophy, and more.

Do you worry about policy-makers overreacting to the He case, and possibly overregulating the use of CRISPR and other gene-editing technologies in a way that may stifle their potential?

No, policy-makers can strike the right balance as they have with other disruptive technologies that have helped move society forward. Currently, under the federal Dickey-Wicker Amendment, making permanent edits to the human germline is illegal in the United States, and the National Institutes of Health is forbidden from funding this type of research.

What do you wish policy-makers would focus on when it comes to CRISPR?

Policy-makers, with the counsel of scientists and bioethicists, have the opportunity to establish an enforceable framework for responsible and accountable management of CRISPR technology.

The World Health Organization has an expert advisory committee looking at governance and oversight of human genome editing, and the US National Academy of Sciences, the US National Academy of Medicine, and the Royal Society of the United Kingdom are leading an international commission to develop a framework for assessing potential clinical applications of human germline genome editing. What do you hope will emerge from these efforts?

Ultimately, we need an enforceable framework, and these organizations are critical in bolstering the effort by pushing government regulators to engage, lead, and act.

We are seeing progress, which is heartening. In July 2019, WHO issued a statement requesting that countries end any human germline editing experiments in the clinic for the time being, and in August 2019, announced the first steps in establishing a registry for such future studies. These directives from a global health authority now make it difficult for anyone to claim that they did not know or were somehow operating within published guidelines.

Do the reports of a Russian scientist's pursuit of embryonic gene editing make you nervous?

Yes, the scientist Denis Rebrikov's approach is concerning. He has publicly said that he is waiting for regulatory approval before implanting any edited embryos. A remaining concern is the edit he is planning to make that would enable deaf couples to produce hearing babies. This is not a modification where there is consensus that it is medically necessary.

Human germline editing has global implications. How should the scientific community think about governing human germline editing on a global scale if regulations are always country specific?

Scientists around the globe are constantly collaborating and learning from one another. The self-governance approach failed in the case of He Jiankui, but the vast majority of researchers are acting ethically and many are engaged in a deeper public conversation about how to establish strong safeguards, encourage a more deliberate global approach, and build a viable path toward responsible use.

You have actively participated in discussions about the scientific, medical, ethical, and policy implications of CRISPR. What role do individual scientists, or the wider scientific community, have in helping to ensure that new discoveries are applied responsibly for the benefit of society?

Scientists need to play their part to make time for conversations with the public in their already busy schedules. These ethical concerns are among the most important considerations for every researcher.

Scientists are equipped to not only advance ongoing scientific research but also guide the public conversation. Individuals and the scientific community alike have a responsibility and opportunity to help shape future research in an ethical manner. Likewise, the public has a role to play in ensuring that discussion of CRISPR technologies, and scientific methodology and discovery in general, takes place.

Anything else you would like people to know about the current state of genome-editing science or its implications for public policy?

Curiosity-driven research funded by taxpayers and nonprofit organizations produced the CRISPR/Cas9 technology and continues to drive the field forward. This work has spawned numerous commercial ventures, creating jobs that focus on applying genome editing technology to advance human health, agriculture, and industrial biotechnology. At a time when people and the planet need CRISPR-derived solutions, we must ensure the technology's long-term viability by applying it responsibly and allowing it to be fairly assessed by those in need.

Jennifer Doudna *is a professor of chemistry and molecular and cell biology at the University of California, Berkeley. She is an investigator with the Howard Hughes Medical Institute, a senior investigator at Gladstone Institutes, and the executive director of the Innovative Genomics Institute. She cofounded and serves on the advisory panel of several companies that use CRISPR technology, including Inari, Synthego, Mammoth Biosciences, and Caribou Biosciences.*