China, Unhampered by Rules, Races Ahead in Gene-Editing Trials

U.S. scientists helped devise the Crispr biotechnology tool. First to test it in humans are Chinese doctors

A cancer patient at Hangzhou Cancer Hospital goes through a procedure that includes infusing his own cells after genetic editing using Crispr. PHOTO: QILAI SHEN FOR THE WALL STREET JOURNAL

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HANGZHOU, China—In a hospital west of Shanghai, Wu Shixiu since March has been trying to treat cancer patients using a promising new gene-editing tool.

U.S. scientists helped devise the tool, known as Crispr-Cas9, which has captured global attention since a 2012 report said it can be used to edit DNA. Doctors haven't been allowed to use it in human trials in America. That isn't the case for Dr. Wu and others in China.

In a quirk of the globalized technology arena, Dr. Wu can forge ahead with the tool because he faces few regulatory hurdles to testing it on humans. His hospital's review board took just an afternoon to sign off on his trial. He didn't need national regulators' approval and has few reporting requirements.

Dr. Wu's team at Hangzhou Cancer Hospital has been drawing blood from esophageal-cancer patients, shipping it by high-speed rail to a lab that modifies disease-fighting cells using Crispr-Cas9 by deleting a gene that interferes with the immune system's ability to fight cancer. His team then infuses the cells back into the patients, hoping the reprogrammed DNA will destroy the disease.

In contrast, what's expected to be the first human Crispr trial outside China has yet to begin. The University of Pennsylvania has spent nearly two years addressing federal and other requirements, including numerous safety checks designed to minimize risks to patients. While Penn hasn't received final federal clearance to proceed, "we hope to get clearance soon," a Penn spokeswoman said.

“China shouldn’t have been the first one to do it,” says Dr. Wu, 53, an oncologist and president of Hangzhou Cancer Hospital. “But there are fewer restrictions.”

Dr. Wu Shixiu, who is leading a Crispr trial at Hangzhou Cancer Hospital. PHOTO:HANGZHOU CANCER HOSPITAL

In traditional drug development, too, human-trial rules can differ among countries. But China’s foray into human Crispr trials has some Western scientists concerned about the unintended consequences of using the wholly new tool—such as harm to patients—which could set back the field for everyone.

Western scientists the Journal interviewed didn’t suggest America’s stringent requirements should be weakened. Instead, many advocate an international consensus on ethical issues around a science that makes fundamental changes to human DNA yet still isn’t completely understood.

Out of the Gate

China has gotten a jump on the U.S. in human trials of Crispr-Cas9. It is the only country known to have conducted tests on humans.

Note: The list represents information that appears on clinical trials.gov or through investigators and companies but may not be comprehensive.

Source: ClinicalTrials.gov

“How do we make sure everyone is under the same tent?” says Jeffrey Kahn, director of the Berman Institute of Bioethics at Johns Hopkins University. With Crispr science still uncertain, “we need to be talking to each other internationally.”

There is little doubt China was first out of the block testing Crispr on humans. Nine trials in China are listed in a U.S. National Library of Medicine database. The Wall Street Journal found at least two other hospital trials, including one beginning in 2015—a year earlier than previously reported. Journal reporting found at least 86 Chinese patients have had their genes edited.

The trials align with China’s industrial policy. As part of its drive to place China on the global stage in a multitude of industries, Beijing in a 2016 five-year plan highlighted gene editing. Many of the Crispr trials emerged after that call-to-arms.

Carl June, lead scientist for the Crispr research team at Penn, says China could beat the U.S. to apply medical technologies such as Crispr pioneered in the West. “We are at a dangerous point in losing our lead in biomedicine,” he says. There is a “regulatory asymmetry” between America and China, Dr. June says, but Crispr science is so new “it is hard to know what the ideal is between moving quickly and making sure patients are safe.”

A Kedgene lab technician performs extraction processes on blood from a cancer patient.PHOTO: QILAI SHEN FOR THE WALL STREET JOURNAL

In Europe, too, trials haven't started. Crispr Therapeutics AG , whose founders include a scientist associated with the tool, announced in December it had filed with the European version of the U.S. Food and Drug Administration to open a clinical trial in Europe. Regulators are reviewing the application, and the company plans to start this year, a spokeswoman says.

Crispr emerges

Crispr, for Clustered Regularly Interspaced Short Palindromic Repeats, serves as the immune system in bacteria. In 2012, a team led by scientists in the U.S. and Austria published a paper demonstrating how they reprogrammed a particular Crispr system to enable gene editing.

The new tool—called Crispr-Cas9 after the natural system it uses—acts like molecular scissors, letting scientists cut or repair DNA. In 2013, U.S. scientists used it to edit the genome of human cells in the lab.

Rewriting the Code

Scientists can use the gene-editing technology called Crispr-Cas9 to correct disease-causing mutations.

Source: Innovative Genomics Initiative John Gould / The Wall Street Journal

The technology is easier to use than other gene-editing methods and less expensive. Lab experiments have shown it can correct some glitches that cause incurable diseases. Crispr has spurred heavy investment and a proposed Jennifer Lopez-produced television thriller.

Rewriting life's building blocks, however, is fraught with scientific and ethical quandaries. One: Crispr might make unintended irreversible changes in people that may not emerge for years.

A new paper from Stanford University suggests many people may have pre-existing immunity to Cas9 proteins and that some Crispr therapies might not work or could spark a dangerous immune reaction.

Dr. Wu agrees risks could surface, calling Crispr "a two-edged sword." Some "see the potential damage," he says. "We see the potential benefits." He says speed is critical because his patients face imminent death. "If we don't try, we will never know."

None of the Chinese trials has published results. While Dr. Wu and other doctors say some patients' conditions improved, at least 15 of the known 86 patients have died of what doctors in the trials say were their diseases.

At first, it looked as if the U.S. would be out in front. The Penn-sponsored Crispr trial was among the first to publicly surface in 2016. The trial targeted patients with multiple myeloma, sarcoma and melanoma.

Later in 2016, news reports said a Chinese hospital had begun the world's first Crispr trial. In fact, it wasn't first—No. 105 Hospital of the People's Liberation Army in Hefei began testing Crispr on patients in 2015, says Liu Bo, who leads that trial.

A Chinese startup, Anhui Kedgene Biotechnology Co., pitched Crispr to the military hospital, say Dr. Liu and Kedgene, offering to apply the tool in Kedgene's lab. Doctors recruited participants, taking their blood and reinfusing edited cells.

"The doctors don't understand gene editing," says Mandy Zhou, who co-founded Kedgene in 2015 and trained medical students on how to use Crispr. "We have to do this together."

Early transfusions at the military hospital shrank some tumors, Dr. Zhou says. She teamed with Anhui Provincial Hospital in Hefei for another trial in 2016. There, participants such as Zhang Jianmin, 45, are showing signs of improvement, says his doctor, Wang Yong. Years of chemotherapy failed to stop his nasal cancer. Within months of receiving Crispr infusions, his nasal tumor shrank, says Dr. Wang, who is involved in the trial.

Dr. Mandy Zhou of Kedgene, a startup working with Dr. Wu in his Crispr trial at Hangzhou Cancer Hospital. PHOTO: QILAI SHEN FOR THE WALL STREET JOURNAL

"If I continue to get better, you have to believe in science," Mr. Zhang said from his hospital bed in September. He is alive and doing well, Dr. Wang says.

Tale of two trials

Dr. Zhou last year approached Dr. Wu, proposing another trial with Kedgene doing the gene editing in its lab 250 miles away.

Dr. Wu says he was eager. He needed approval only from his hospital ethics committee. Its role is similar to U.S. institutional review boards that examine proposals and assess risks.

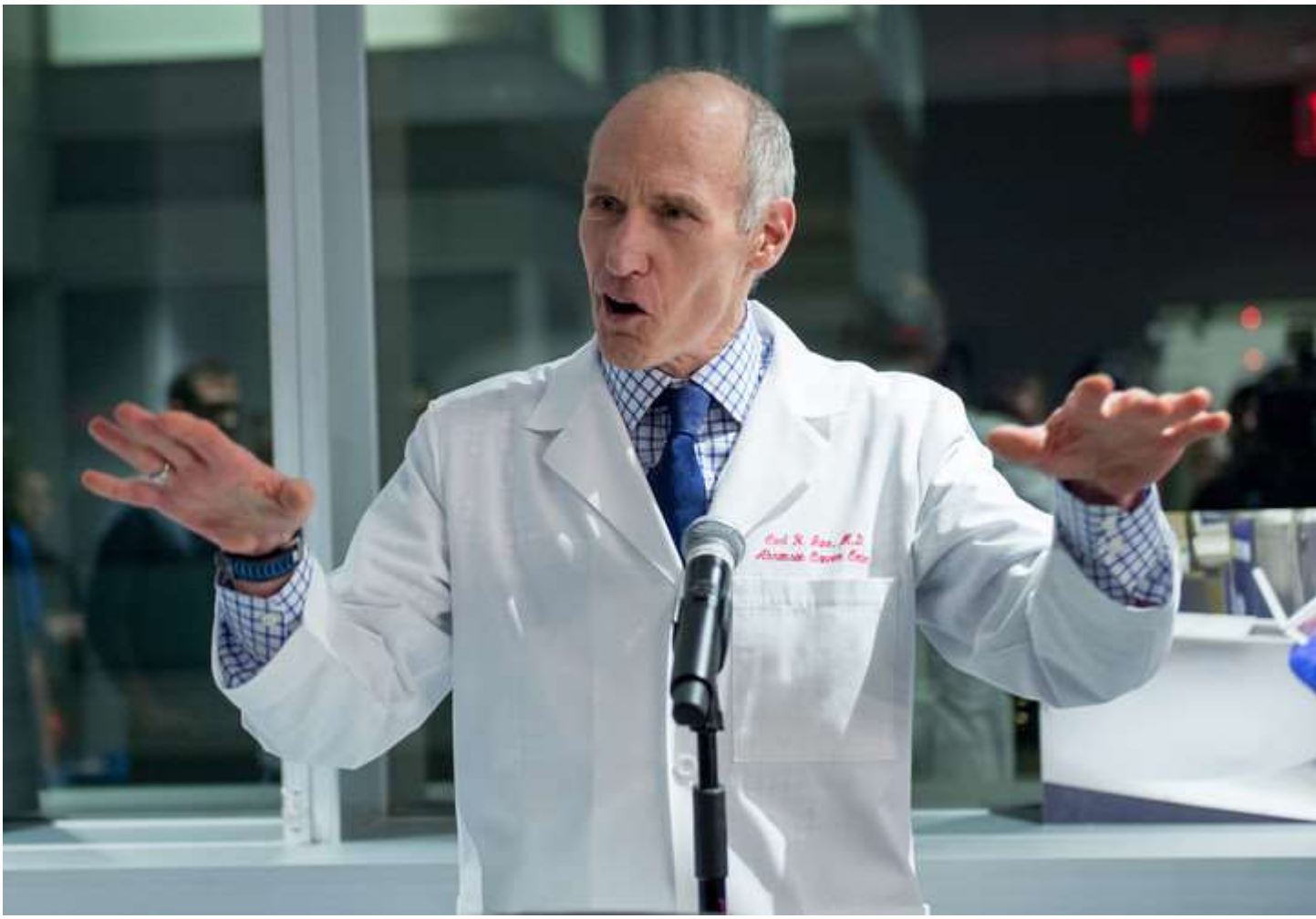
In the U.S., investigators must also apply for FDA review before a human trial can proceed. A regulation of China's health ministry, which is responsible for medical affairs, authorizes a hospital's ethics committee to approve research on humans. The ministry didn't respond to requests for comment.

Reviewing Dr. Wu's proposal was a committee appointed by his hospital, comprising nine people including doctors from the hospital, a lawyer and a former cancer patient, Zheng Xiaomin. The seven who showed up sifted through a roughly 100-page proposal and watched a PowerPoint presentation, panel members say.

Ms. Zheng says the proposal, which she received a day in advance, "was too much to finish reading." She says she "didn't understand the academic details" but did ask about side effects and was told they were mild.

Deng Qinghua, a radiologist on the panel, says he voted in favor because the gene that was going to be cut out had been targeted before in successful cancer therapies—suggesting a lower risk. The application passed unanimously in one afternoon.

Penn's Dr. June was navigating a more rigorous process.



Dr. Carl June, lead scientist of the University of Pennsylvania's Crispr research team.PHOTO: PENN MEDICINE

To get a go-ahead from his hospital's review board and the FDA, he first sought an assessment by a U.S. National Institutes of Health advisory committee. The NIH set up the committee 40 years ago in the wake of public concern about new gene technologies.

At a June 2016 meeting, the NIH panel asked Penn's team to strengthen warnings to patients explaining that the procedure was experimental and that ill effects might be irreversible, according to committee members and a meeting transcript.

Mildred Cho, a Stanford University bioethicist on the committee, requested Penn describe the trial as "gene transfer" instead of "gene therapy," which she says implied effective treatment, not experimentation. The investigators complied.

“We want to make sure everyone knows this is an experiment and not a cure,” says Laurie Zoloth, dean of the University of Chicago Divinity School and a bioethicist on the committee. “Especially with end-stage cancer, the intervention can be grueling. Experiments can fail, and in ways that can be terrible.”

At the time of the NIH hearing, Dr. June’s lab had run a variety of tests to see if Crispr made unintended cuts in cells. He says the FDA wanted still more. The FDA declined to comment on the process.

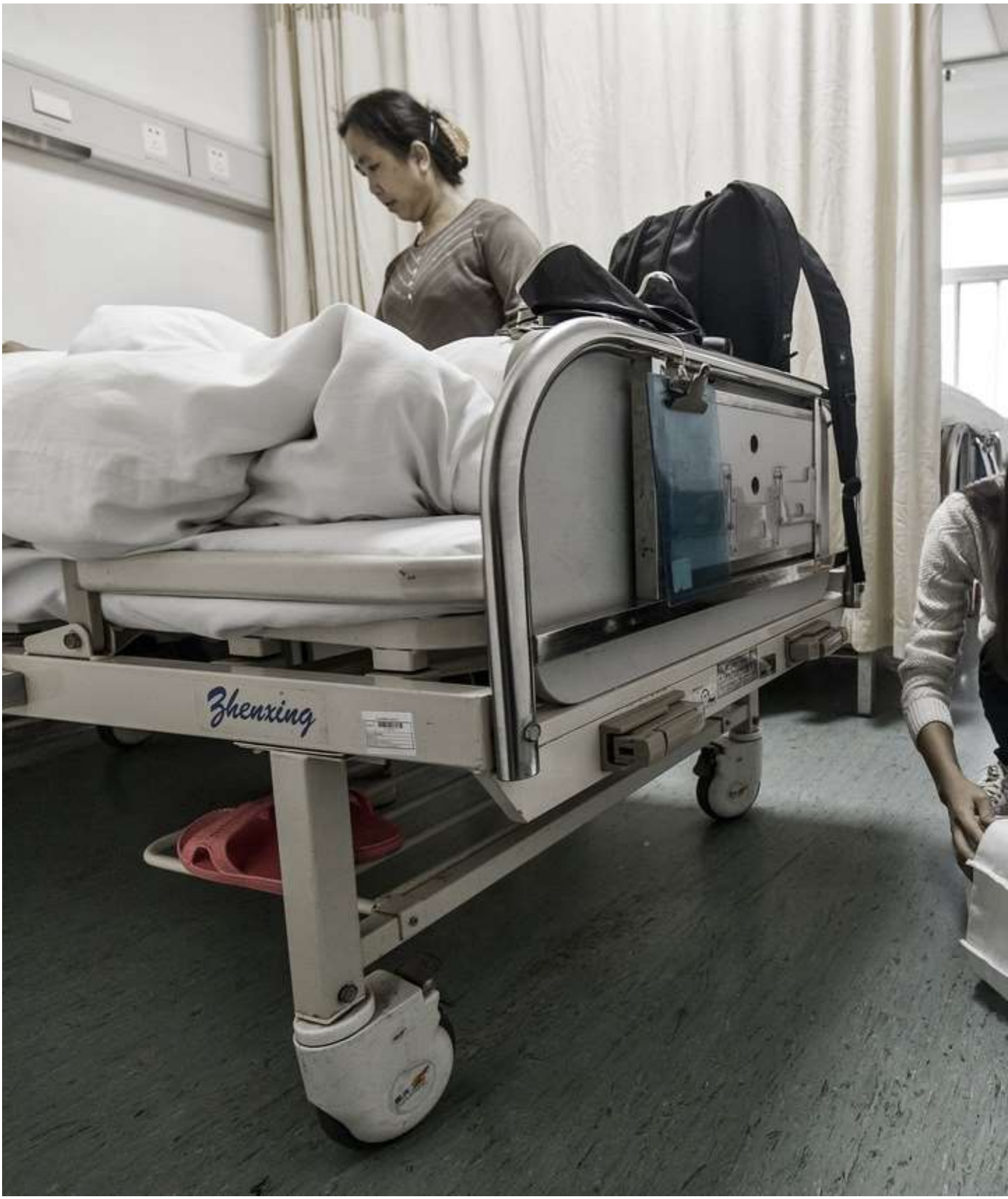
Dr. Wu says he didn’t have the time to do such tests because his terminally-ill patients needed treatment urgently.

The NIH advisory committee allowed the Penn team to proceed. The researchers then spent over a year in discussions with the FDA, providing information and answering requests. Penn’s ethics review was completed in late 2017, and Penn is awaiting final FDA clearance, the Penn spokeswoman says. Dr. June says he expects clearance as early as this month.

After the Penn trial begins, it will again face different standards from Dr. Wu’s. In enrolling patients, Penn researchers must use consent documents examined by the FDA and the hospital institutional review board. Cases involving patients harmed during biomedical research “set in motion a chain of events that ended up with the regulatory system we have,” says Stanford’s Dr. Cho.

Dr. Wu’s consent letters briefly mention gene engineering. He says he tells patients his trial is aimed at modifying their immune systems and doesn’t dwell on the fact he is using an experimental tool. His explanation to participants, he says, varies based on their education.

“The Chinese patients will sign the consent letter,” says Kedgene’s Dr. Zhou. “But mostly they listen to what doctors tell them.”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Blood from a cancer patient is packed and transported from the Hangzhou Cancer Hospital to a Kedgene lab in Hefei, China, where technicians edit the genes of the immune cells in the blood. The hospital then re-infuses altered cells back into patients. PHOTOS: QILAI SHEN FOR THE WALL STREET JOURNAL(4)

Penn also must report deaths. An FDA spokeswoman says investigators must immediately inform a trial's sponsor of serious adverse events, such as death, regardless of whether they are trial-related. The sponsor must then notify the FDA.

Seven of Dr. Wu's patients have died, among 15 known deaths across Kedgene's three trials, say Dr. Wu and other doctors involved. Dr. Wu says the deaths in his trial were due to patients' diseases and not related to Crispr, so he wasn't required to report them to his ethics committee.

China's health ministry requires researchers report "adverse events" to their ethics committees. Dr. Wu says deaths unrelated to the trial aren't seen as adverse events. Wei Jia, who is leading a separate Crispr trial at Nanjing University's Drum Tower Hospital and isn't involved with Kedgene, says any fatality in a trial is considered an adverse event.

Dr. June says the Penn study will test whether Crispr is safe and "isn't designed to see if we can cure patients." The researchers plan to test Crispr on one patient, wait a month to make sure there aren't adverse reactions, then try it on two more.

Dr. Wu says he sees saving patients' lives as paramount. He began by testing Crispr on three patients and has modified genes of more than a dozen. He says he is planning other trials with lung-cancer and pancreatic-cancer patients.

Not all China's Crispr trials were approved as easily. Dr. Liu, the principal investigator in what appears to be the world's first experiment, says his ethics-committee reviewers took months to approve his trial after asking for supplementary information.

More U.S. Crispr trials are expected to open in the next 18 months, led by publicly traded companies started by scientists associated with the tool.

The University of Chicago's Dr. Zoloth says she hopes countries will devise international Crispr standards, sharing results and ethics. "We need to talk collectively about what it means in science to prove something," she says, "and about what it means to protect someone, too."

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