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IDEAS AND OPINIONS

Calls for Caution in Genome Engineering Should Be a Model for Similar Dialogue on Pandemic Pathogen Research

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Recently, 18 leading researchers in science and biotechnology published an unprecedented statement in *Science* calling for great caution in the application of new CRISPR/Cas9 (clustered regularly interspaced short palindromic repeats/CRISPR-associated protein 9) technologies to editing of the human germline (1). These technologies allow molecular biologists to modify genomes in ways that were previously difficult or impossible, creating the potential to treat disease by correcting genetic defects. However, these methods also allow genome modification in the germline that would be passed on to the organism's progeny.

The statement called for the development of a thorough understanding of ethics and safety around CRISPR/Cas9 germline editing and advised against certain kinds of experiments involving human germline modification until an appropriate framework is constructed with input from relevant stakeholders and societal discussion. Remarkably, the inventors of the technology are leading this effort to bring scrutiny and restraint. An overlapping group of scientists and science policy experts (including one of the authors of this article) made similar calls last year (2, 3) related to other applications of CRISPR/Cas9, called "gene drives," that could alter plant and animal populations. These earlier calls detailed the technical feasibility of gene drives in advance of laboratory development while emphasizing possible risks and ethical complications as well as benefits. They also highlighted ways in which the safety of gene drive research and applications could and should be enhanced by the use of containment measures that are robust against human error.

Clinicians, public health experts, and representatives of the public should similarly be involved in examining the advisability of performing certain classes of experiments intended to create potential pandemic pathogens (PPPs). In particular, a similar process could develop policies for how these communities should be engaged in discussions about research intended to create PPPs, such as novel influenza strains that are mammalian-transmissible and highly pathogenic.

These types of studies incur risks, and these multiple perspectives could identify approaches to reducing that risk. Initiating broadly inclusive discussions is crucial to enhancing public confidence in scientists as responsible stewards of powerful new technologies and worthy recipients of public funding to support such research. The article on CRISPR/Cas9 human germline editing stated that "the most important lesson learned [from the dawn of the recombinant DNA era] was that public trust in science ultimately begins with and requires ongoing transparency and open discussion".

In the event of an accident, PPPs could spread widely and ultimately infect populations far removed from the source. In contrast to CRISPR/Cas9 human germline editing and gene drive technologies, research aiming to create novel, virulent, and transmissible influenza strains was initially undertaken without any effort to seek public permission or call attention to the risks and ethical complexity of the topic. Many virologists, biologists, ethicists, clinicians, and public health experts not involved in such experiments (4–8) have called for a risk assessment and widespread discussion "to identify approaches to achieve global public health goals of defeating pandemic disease while assuring the highest level of safety" (8).

The InterAcademy Panel Statement on Biosecurity (9), adopted by 74 national academies of science, states that "scientists have an obligation to do no harm. They should always take into account the reasonably foreseeable consequences of their own activities." The foreseeable consequences of creating novel, transmissible, virulent pathogens include a probability—quantifiable on the basis of existing data on laboratory accidents—that a laboratory worker will become infected and a probability that such an accidental infection would spark a global pandemic (6). Given the unprecedented potential harm to human welfare (and, not incidentally, the credibility of science) that such spread could cause, scientists performing gain-of-function experiments on influenza and other PPPs should follow the lead of colleagues in other areas of life sciences in acknowledging that some of these experiments may pose unacceptable risks and should not be pursued in the absence of adequate mitigation measures.

The U.S. government has established a funding moratorium on PPP research (10), a central component of which will be a risk assessment intended to help provide quantitative input to deliberations. The statement on CRISPR/Cas9 germline editing (1) articulated additional steps that have clear parallels in the consideration of PPP research, calling on countries to strongly discourage germline editing in humans "while societal, environmental, and ethical implications of such activity are discussed among scientific and governmental organizations . . . this will enable pathways to responsible uses of this technology, if any, to be identified."

For PPP research, few countries have thus far engaged directly in dialogue or begun evaluations of these controversial approaches, now years after their initiation. Those that have, including the United States,

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have seldom included some of the most relevant communities, including clinicians and public health experts who would need to lead efforts to reduce the harms of an accident or deliberate misuse. Even fewer members of the nonscientific public have been represented despite the possibly global consequences of a PPP release. Scientific discussions of the benefits of PPP research have included claims of great benefit for vaccine development and public health surveillance, yet vaccine manufacturers, infectious disease clinicians, and researchers as well as public health experts have played only a small part in the debate. Nor is there agreement on the magnitude of potential dangers that must be considered in the calculation of the value and safety of the work. No internationally representative group has been convened to consider these issues. Scientists pursuing research on PPPs should support all of these steps, as should the greater international scientific, clinical, and public health communities.

It is commonly accepted by scientists and others that ethical, safety, and animal welfare considerations limit what kinds of experiments may legitimately be performed, and even prohibit some studies that could produce scientifically valuable information. For PPPs, human germline editing, gene drives, and other technologies with the potential to affect humanity in uncertain and highly consequential ways, similar deliberations on appropriate transparency, safeguards, and limits—deliberations that include the appropriate scientific, clinical, and public health communities—are now clearly warranted.

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