The current kerfuffle around the use of CRISPR/Cas9 and other gene editing technologies in human germline research is the latest in a series of related controversies at the intersection of science, medicine, and ethics [1]. Soon after a prominent ad hoc group of scientists called for a moratorium on clinical applications of germline gene editing [2], a research group from China published an article that described the genetic modification of human embryos [3]. Although these experiments were performed in nonviable, triploid embryos that were neither intended nor suitable for clinical use, the work nonetheless demonstrates how the prospect of manipulating the human germline elicits hopes and fears and triggers moral debates. Are such concerns warranted? Should research be put on hold while ethical and legal debates take place? Similar tensions arose in the past with recombinant DNA technology, assisted reproductive technologies, gene transfer research, human cloning, embryonic stem cell research, and mitochondrial replacement therapy. What, if anything, might be learned from these prior debates?

CRISPR/Cas9 is an efficient, inexpensive, and precise method to edit genes at the level of individual nucleotides, which enables the exploration of myriad scientific questions. Moreover, it promises potential new treatments for many human diseases: HIV infection has been targeted, for example, by editing the CCR5 receptor in somatic cells using TALEN (transcription activator-like effector nucleases) [4]. Of course, the prospect of altering the germline opens an even greater range of possibilities. For example, germline editing might be the only means of treating genetic diseases, which are otherwise fatal in utero. In addition, gene editing technologies could potentially supplant the need for assisted reproductive technologies in those who are affected by certain genetic diseases. Correcting the faulty gene in the embryo or in gametes could minimize the use of burdensome procedures such as oocyte stimulation and selective abortion following prenatal diagnosis. Moreover, the use of gene editing technologies in conjunction with stem cells, such as induced pluripotent stem cells, might make it possible to generate gametes for reproductive purposes and correct errors in their genome, thus precluding or minimizing the need for oocyte donation.

While such applications might at first glance be appealing and beneficial to those who are directly affected—and the clinicians caring for them—the potential hazards may be substantial. For instance, there are scientific concerns that CRISPR/Cas9, TALEN or Zinc Finger nucleases could inadvertently target other loci in the genome and that such unanticipated genetic manipulations could alter biological functions in problematic ways. In addition, the potential of using gene editing technologies in the human germline adds considerable moral complexity. After all, deliberately manipulating the human germline has generally been viewed as unacceptable, and it is prohibited in many parts of the world [5]. Furthermore, if gene editing technologies are combined with pluripotent stem cells for clinical purposes, the ethical territory is not well charted. Such considerations undoubtedly contributed to the proposed moratorium on clinical experimentation using gene editing technologies.

It is informative to review the global landscape of assisted reproductive technologies in understanding the need for a moratorium. First, although such technologies raise a series of important ethical and clinical challenges, their clinical use is regulated and overseen to variable degrees around the world [6], which results in differences in professional practice. Similarly, in some jurisdictions, including the USA, research related to human embryos and some assisted reproductive technologies can escape substantial oversight, despite the inherent ethical issues associated with it [7]. Arguably, there is currently no uniform, global approach to ensuring that novel clinical approaches using reproductive technologies are scientifically, medically and ethically sound. This stands in contrast to most therapeutic interventions which are expected to be carefully evaluated along with established oversight processes that rest on widely shared ethical principles as described, for example, in the Belmont Report.

Some of the scientific concerns about manipulating the human germline with gene editing technologies will likely be addressed through more research and development to increase safety and efficacy. Regarding the related ethical issues, it is helpful to be aware of prior discussions to better understand what is at stake. There are several arguments against manipulating the human germline. To name just a few, these include that it is unacceptable to provide intergenerational consent, that the consequences are impossible to predict, and that such manipulations pose a threat to human dignity [5,8,9]. Despite their appeal, however, these and other arguments alone are not necessarily sufficient to argue against human germline manipulation. For instance, while intergenerational consent is unfeasible, it has been argued that such a concern may be misplaced since “germline manipulations that effect [sic] future generations are not different ethically from any other human decisions that effect [sic] future generations” [10]. Similarly, arguments concerning the inability to predict consequences may not be relevant for well-intentioned research to improve the current state of affairs, but rather highlight the need for more data about the safety of proposed interventions. Finally, critical questions about human
dignity cannot be readily answered in a uniform way owing to profoundly different notions of the concept of dignity. Yet, there are also non-irrefutable reasons for proceeding with germline interventions. These would include clinicians’ professional responsibility to choose the optimal treatment for their patients and the right of individuals to have their reproductive autonomy respected [9].

These tensions have been addressed for other biotechnologies in the past. For instance, they were discussed in detail for the possibility of conducting in utero gene transfer, which has the potential to inadvertently affect the germline. In this case, a major conference was convened to discuss two pre-protocols for gene transfer in attempt to cure alpha-thalassemia (which is fatal in utero) and adenosine deaminase deficient-severecombined immunodeficiency (for which there are treatment alternatives). After considering these issues in depth, the Recombinant DNA Advisory Committee that is responsible for oversight of gene-transfer research in the USA, decided not to permit such research to move forward in 2002 [7].

In view of the unanswered scientific questions and inherent moral issues concerning germline gene editing in general, it is essential to conduct public discussion and deliberation about these emerging technologies. However, given the repetitive nature of these types of debates, it would be valuable to consider not only the issues raised by the technology du jour, but rather seek to articulate general principles so that they might be applied as new technologies with the ability to edit the germline are being developed. Discussions on gene editing in particular that are planned so far include efforts facilitated by academicians such as the Hinxton Group and entities with broad convening power such as the US National Academy of Medicine (formerly the Institute of Medicine). Such efforts can help to underscore the normative aspects of science, separate facts from fiction and provide frameworks to parse scientific practices that are acceptable from those which are unacceptable. Scientists, clinicians, and those affected by conditions that might be ameliorated by germline editing should engage in such efforts to help ensure the integrity of not only the processes, but also the outcomes.

Although it is impossible to forecast the results of such deliberations, given the historical precedents set by gene-transfer research and embryonic stem cell research, it is likely that there will be at least some calls for special oversight of research that could possibly lead to clinical applications. After all, translating gene editing from the bench to the bedside will necessitate overcoming a succession of scientific, technological, and ethical hurdles. Given the legitimate concerns about its safety, aligned with the lack of political and moral consensus about these technologies, especially in the germline, establishing an oversight mechanism seems prudent.

Such an approach to oversight should have representation from a broad range of stakeholders with legitimate interests and expertise to meaningfully engage in a fair process. While it is unlikely to foster global consensus around all of the inherent issues, having an oversight system in place should help to address and manage the most important concerns and might even lead to generating some globally accepted standards akin to most research with human subjects. Regardless, developing and implementing efficient oversight and policies will require resources and will inevitably raise questions about what, if anything, is exceptional about this sort of research. Unfortunately, existing mechanisms for similar types of oversight—research ethics committees, stem cell oversight committees—do not seem to be appropriately suited to perform review for germline editing, given their composition and operating guidelines. In view of the associated moral stakes, scientific promise and public interest, however, establishing widely accepted approaches toward the oversight of the science seems to be a prudent path forward.

References