

## HEALTH LAW

### What Is Prudent Governance of Human Genome Editing?

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#### Abstract

CRISPR technology has made questions about how best to regulate human genome editing immediately relevant. A sound and ethical governance structure for human genome editing is necessary, as the consequences of this new technology are far-reaching and profound. Because there are currently many risks associated with genome editing technology, the extent of which are unknown, regulatory prudence is ideal. When considering how best to create a prudent governance scheme, we can look to 2 guiding examples: the Asilomar conference of 1975 and the German Ethics Council guidelines for human germline intervention. Both models offer a path towards prudent regulation in the face of unknown and significant risks.

#### Introduction

In recent years, there has been a significant debate regarding human genome editing. The debate has intensified with the advent of CRISPR<sup>1,2</sup> and the births of twin girls in China whose genomes were edited at the embryo stage using CRISPR technology.<sup>3</sup> This new technology has certain risks of unknown magnitude coupled with potentially far-reaching consequences—ranging from safety and efficacy concerns, to more nuanced social and ethical implications, to globally profound implications, such as the shaping of human evolution. The potential risks and consequences of genome editing have raised concerns around the world.

Debates are currently unfolding about how best to regulate this technology.<sup>4,5,6</sup> Regulation can take many forms, which may include a moratorium on the technology's use or assessment and enactment of restrictions and standards by regulatory agencies. For the purposes of this article, I refer to governance of genome editing technologies in the broad sense, which includes both permissibility and regulatory burdens. When considering a prudent and ethical form of human genome editing governance, guidance can be obtained by reflecting on how experts dealt with similar bioethical conundrums in the past while also considering recent ethical analyses offered by various national committees and councils presently working on the issue. In this article, I detail 2 such guiding examples: the International Conference on Recombinant DNA Molecules, held at Asilomar, California, in 1975<sup>7</sup> and the German Ethics Council's recent report<sup>8</sup> on human

germline editing. The Asilomar conference provided one template for how to address governance and risk associated with a new biotechnology (recombinant DNA), and the German Ethics Council built on this template by offering a model of prudent governance of biotechnologies related to human germline genome editing.

### **Human Genome Editing**

Human genome editing is the making of additions, deletions, or alterations to the human genome.<sup>9</sup> There are a variety of techniques to accomplish this goal, most involving clustered regularly interspaced short palindromic repeats (CRISPR) and a nuclease enzyme, such as Cas9, that can cleave DNA molecules. The CRISPR-Cas9 technique has the potential to revolutionize genome editing, primarily because CRISPR is “easy to use, low in cost, and a more precise tool for genetic engineering than earlier tools.”<sup>10</sup> Now that editing the genome can be accomplished with greater ease and precision, questions of how to ethically and safely allow such alterations to the genome have become immediately relevant.

When analyzing these questions, it is important to recognize 2 distinctive applications of genome editing: somatic and germline. In somatic genome editing, edits are “limited to the treated individual and would not be inherited by future generations.”<sup>9</sup> By contrast, germline genome editing involves editing embryos or gametes (sex cells), which, if transferred for gestation, would enable the gene edits to be heritable.<sup>4</sup> Because germline interventions can affect future generations, once made, they can have a ripple effect of great magnitude, which may include the potential to shape human evolution.<sup>11,12</sup> The distinction between somatic and germline editing thus has significant ethical implications.

Beyond this key distinction, the potential risks and consequences—both to individuals and society—of human genome editing are relevant to ethical considerations of nonmaleficence, beneficence, justice, and respect for autonomy and are thus also relevant to the creation of an appropriate regulatory model. Because genome editing technology is at its beginning stages, it poses safety risks, the off-target effects of CRISPR being one example.<sup>13</sup> Another issue is whether gene editing is done for therapeutic or enhancement purposes. While either purpose can prove beneficial, enhancement has potential for abuse.<sup>14</sup> Moreover, concerns exist that genome editing for enhancement can thwart social justice, as wealthy people will likely have greater ability to enhance their genome (and thus presumably certain physical and mental characteristics), furthering social and class divides. With regards to germline editing, a relevant concern is how, during the informed consent process, to respect the autonomy of persons in future generations whose genomes are modified before birth. The questions raised by genome editing are profound, and the risks—both to the individual and to society—are evident. Left without proper governance, significant harmful consequences are possible.

Therefore, at this stage, a prudent regulatory scheme for human genome editing is called for. Below, I detail 2 examples (the Asilomar conference and the German Ethics Council's report regarding human germline editing) that each provide a prudent approach to governance.

### **Two Prudent Regulatory Models for Human Genome Editing**

*Asilomar conference of 1975.* The early 1970s saw the rise of recombinant DNA (rDNA) technology, which involves the artificial combination of DNA from different organisms. Famed Stanford researcher Paul Berg was doing rDNA research with a virus known to cause tumors, which aroused fear in the scientific community that "introduced genes could change normally innocuous microbes into cancer-causing agents or into human pathogens, resistant to antibiotics or able to produce dangerous toxins."<sup>15</sup> In response to these concerns, scientists created a de facto worldwide moratorium on rDNA research, which resulted in the Asilomar conference convening in 1975 (spearheaded by Paul Berg and other leaders in the field) to further address how the scientific community should proceed with rDNA research. Indeed, the idea behind the conference, referred to now simply as Asilomar (nicknamed after the conference's famed location on the California coastline), was that a congregation of experts could set "their terms of reference regarding risk and governance."<sup>16</sup> The conference ultimately decided to lift the moratorium and agreed on "safety guidelines of varying stringency according to the degree of risk."<sup>15</sup> These safety guidelines ultimately served as the basis of the official National Institutes of Health guidelines with regards to rDNA research.<sup>15,17</sup> Although over time, the risks of rDNA technology proved to be unfounded,<sup>15</sup> these guidelines have been deemed a success story in organized risk management and its broader influence on governmental regulations.<sup>18</sup> The influence of the conference is still felt today, as a similar congregation of geoengineering experts has been dubbed an "Asilomar moment."<sup>16</sup>

While Asilomar has been largely heralded as a success, it has not been without its critics. One of the strongest criticisms is that the conference was largely attended by other scientists in the field and "did not cast a wide net outside the scientific community."<sup>19</sup> As such, some have argued that this limited the "narrative" of the conference to technical safety issues, which excluded governance applications and broader societal and ethical aspects of the technology.<sup>16</sup> Schäfer and Low note, "Although discussions on the broader societal, political and ethical implications of rDNA technology surfaced during early considerations, such framings never came to dominate the discourse, and risk perception remained limited to technical aspects."<sup>16</sup> Berg and Singer argue that this criticism of Asilomar's "failure to consider the ethical and legal implications" was partly because of a "lack of time" and that the "principal and more urgent concern for those gathered at Asilomar was the possible effects of recombinant DNA on public health and safety."<sup>17</sup> The Asilomar model, as a prudent approach to governance in the face of unknown risks, is a useful guide for governance of human genome editing. As with rDNA at the time, the

true scope of the risk of genome editing is currently unknown and is coupled with potential for negative consequences of global scale.

*German Ethics Council (Deutscher Ethikrat).* In May 2019, the German Ethics Council (Deutscher Ethikrat) released its guidelines on human germline genome editing.<sup>8</sup> The German council recommends that there be a moratorium on human germline editing considering the risks that now exist. The council even goes so far as to call for the moratorium to be internationally binding, which is exceptionally prudent considering the global scale of the risk associated with germline editing. However, the council notes that the moratorium should be revisited and evaluated as new information about the technology comes to light and when risks can be reduced; the council recognizes the ethical support for and beneficial value of the technology and acknowledges that if certain evidential thresholds are attained, germline editing can be ethically performed.

Distinguishing itself from Asilomar, the German Ethics Council highlights ethical and societal considerations beyond a risk-benefit analysis. The German council notes:

The assessment of the permissibility of germline interventions should not be reduced to a mere risk and opportunity analysis. Rather, it should be based on the ethical concepts of human dignity, protection of life and integrity, freedom, non-maleficence and beneficence, naturalness, justice, solidarity and responsibility.<sup>8</sup>

However, the German council notes that safety is still an important consideration: the “prerequisite of permissibility [of germline editing] is, in any case, a sufficient degree of safety and efficacy of such interventions.”<sup>8</sup> Safety and efficacy are merely starting points in the analysis of how to govern the technology’s use; societal and ethical implications must then be considered as well. Hence, the German council recommends the creation of an international agency that would evaluate the “scientific, medical, ethical, legal, societal and political implications of germline interventions in humans.”<sup>8</sup>

The German Ethics Council is not presently alone in providing substantive and thoughtful guidance for genome editing. Other councils and committees, such as the National Academy of Sciences in the United States<sup>9</sup> and the Nuffield Council on Bioethics in the United Kingdom<sup>20</sup> have also provided guidance, and they—countering a major criticism of Asilomar—are based on experts who are not limited to scientists. The advantage of nationally drawn committees and councils like these is that a wide range of experts (ie, experts drawn from the fields of medicine, biology, law, ethics, economics, and the social sciences) can offer a holistic perspective on the issue to a greater extent than a conference comprising mostly one type of expert.

## Evaluating Models

*Asilomar.* Some have argued that Asilomar was not a success in that the risks associated with rDNA did not ultimately come to fruition.<sup>21</sup> However, I disagree with this notion of failure. The key point of Asilomar at the time (and largely the impetus for the conference itself) was that the risks of rDNA were not known; unknown risks spanned a wide spectrum of possibilities. At one end, risk might be nonexistent or negligible; at the other end, risk might be high with substantial consequences. Proof that rDNA technology is low risk (as turned out to be the reality), was one outcome that some Asilomar attendees considered possible.<sup>15</sup> However, their prudence in the face of the unknown dictated the guidelines they put forth. In this regard, I would argue that Asilomar was a success, in that scientists guided themselves by prudence in the face of unknown risk, allowing such guidelines to be malleable with the input of new information. Asilomar can serve as a model for governance and guidance of genome editing today, as genome editing currently presents unknown risks of similar magnitude to those presented by rDNA back in the 1970s. It is possible that the risks of human genome editing debated and discussed today are overblown and that, like rDNA technology, we will find the risks ultimately to be insignificant. However, until we have more information, it is prudent to appreciate the risks given the potentially large consequences of genome editing, especially germline genome editing.

*German Ethics Council.* Building on the example set by Asilomar, the German Ethics Council provides a prudent path forward. But the German council goes beyond Asilomar in adopting an *inclusive strategy* that involves a wide group of stakeholders (ie, not limited to scientists) and also demands that social, legal, ethical, and political implications—in addition to an initial weighing of safety risks—be considered in any analysis of proper governance. Ultimately, the German council recommends a moratorium on the present usage of germline modification, but the council underscores that such a moratorium should not necessarily be permanent, as the germline is not inherently “inviolable.”<sup>8</sup> The council recommends that the moratorium undergo regular review with consideration of whether “minimum safety and efficacy requirements regarding germline interventions have been sufficiently met.”<sup>8</sup> If such a prudent path (ie, one that appreciates the technology’s risks in recommending a moratorium but is also mindful of its benefits in making the moratorium nonsticky and modifiable) can become a true international consensus on how to approach genome editing (particularly germline editing), such a consensus can likely become, in the absence of a binding international agreement, the best possible way to mitigate the technology’s risk on a global scale.

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