

PERSPECTIVE

## Controlling CRISPR Through Law: Legal Regimes as Precautionary Principles

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### Abstract

Since its advent in 2012, CRISPR has spawned a cottage industry of bioethics literature. One principal criticism of the technology is its virtually instant widespread adoption prior to deliberative bodies conducting a meaningful ethical review of its harms and benefits—a violation, to some, of bioethics’ “precautionary principle.” This view poorly considers, however, the role that the law can play—and does, in fact, play—in policing the introduction of ethically problematic uses of the technology. This Perspective recounts these legal regimes, including regulatory agencies and premarket approval, tort law and deterrence, patents and ethical licenses, funding agencies and review boards, as well as local politics. Identifying these legal regimes and connecting them to the precautionary principle should be instructive for bioethicists and policy makers who wish to conduct ethical reviews of new applications of CRISPR prior to their introduction.

### Introduction

CRISPR—the cheap, easy, flexible, and programmable genome-editing technology—has, since its advent in 2012, defined an entire subfield of molecular biology, produced thousands of technical papers describing its myriad applications, and—as here—even inspired its own journal. It has also spawned a cottage industry of bioethics literature, with commentators raising concerns that CRISPR will harmfully alter the evolution of species,<sup>1</sup> usher in an era of “designer babies,”<sup>2</sup> and revive extinct animals, among other applications.<sup>3</sup> To analyze the potential ethical import of these applications, several bioethics associations, such as the Association for Responsible Research and Innovation in Genome Editing (ARRIGE), announced in this journal’s second issue, have been established to “address multiple issues raised by genome-editing technologies used in research and applications within a safe and ethical framework for individuals and society.”<sup>4</sup> Since 2015, scientific academies and government agencies have issued more than 60 “official reports” about the ethics of CRISPR.<sup>5</sup>

While the literature is varied, the general thrust of many of these analyses is the difficulty of controlling ethically problematic uses of CRISPR. Without increased “oversight” of the technology, many commentators have

raised the possibilities of CRISPR contributing to an exacerbation of health inequities,<sup>6</sup> a diminishment of human dignity,<sup>7</sup> and an ossification of technological determinism.<sup>2</sup> To that end, a fair amount of bioethics scholarship on CRISPR has called for a reinvigoration of the “precautionary principle”: a temporary moratorium on certain applications of the technology, as a precaution, until such harms can be reasonably safeguarded against.<sup>8</sup> The implication of these calls is that whatever laws currently serve to regulate CRISPR, the technology is so profoundly transformative that the law cannot adequately police it.

This article takes a different view of the state of the law in regards to CRISPR. A variety of currently existing legal regimes can—and do—control the research and development of CRISPR in ways that robustly further the precautionary principle. Regulatory agencies, such as the U.S. Food and Drug Administration (FDA), have the power to forbid commercial applications of new biotechnologies, such as CRISPR, without prior, stringent proof of safety and efficacy. Tort regimes, as in other contexts, act as deterrents against negligent applications of the technology. Patents and patent licenses can—and are—being used to tamp down on ethically questionable uses of the technology. Funding agencies similarly have significant oversight concerning how the technology

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is used in publicly funded research settings. And, lastly, there is always local politics—democratic restrictions on ethically difficult uses of the technology in certain locations.

As radical as CRISPR may be, currently existing laws and regulations do, in fact, serve to prevent its riskiest excesses, squarely in line with the precautionary principle. To the extent the prescriptive suggestions of bioethics literature on CRISPR call for further application of the precautionary principle, these legal regimes can be used as they currently stand, without crafting new layers of oversight. This article provides a broad overview of these legal regimes—how they operate and how they serve to guard against many of the risks currently prevalent in the bioethics literature surrounding CRISPR. And while this article focuses primarily on the United States, similar regimes outside of the United States are likely to apply as well.

### Premarket Approval and Regulatory Agencies

One of the principal criticisms of CRISPR in the bioethics literature centers on its reinforcement of “technological determinism”: that if an application of technology is technically feasible, its adoption is *fait accompli*.<sup>2,9,10</sup> As applied to CRISPR, this risks using the technology in ways that are unethical, unsafe, or threaten the public weal simply because they are possible. The recent experiments on human embryos by He Jiankui, resulting in the birth of two children in China with CRISPR-mediated genetic modifications, serve as perhaps the strongest warning on the dangers of such an approach.<sup>2</sup> To guard against such an “inexorable tide” of technological advance,<sup>11</sup> a number of bioethicists have suggested a reinvigoration of the precautionary principle, especially as it concerns using CRISPR for therapeutic purposes. This has famously included a call for a temporary global moratorium on human germline modification using CRISPR by some of the technology’s most celebrated scientists.<sup>12</sup>

Here, as elsewhere, the animating principle behind calls for more robust precautionary approaches is that current laws and regulations are not up to the task of assessing the safety of new applications of CRISPR before they become prevalent in the marketplace. Given CRISPR’s global reach, this includes concerns even with adequate domestic laws to prohibit such work, the world will succumb to a technological race to the bottom, with different countries facilitating the very work others find ethically problematic. In truth, however, such assessments are precisely the function of the variety of overlapping regulatory agencies that currently oversee different aspects of CRISPR. For human therapies, of course, the FDA and its international counterparts, such as the European Medicines Agency,

oversee the introduction of virtually all new drugs and biological products into commerce. Given the breadth of the statute giving power to the FDA, the agency’s authority in the area is immensely broad and, when vigorously enforced, extremely powerful.<sup>13</sup> The FDA has stated itself that it considers a variety of uses of CRISPR to fall within its jurisdiction.<sup>14</sup> And while the U.S. Department of Agriculture (USDA) has allowed certain CRISPR crops to reach shelves without a premarket review, it has nonetheless made clear that such crops are subject to its continuing oversight, including its Plant Protection and Quarantine program.<sup>15</sup>

These authorities are, ultimately, precautionary in nature. In the human context, developers of CRISPR therapies are prohibited from publicly introducing their products prior to a robust demonstration of their safety and efficacy.<sup>14</sup> Contrary to the notion that such approvals are inevitable—and thus traffic on the notion of CRISPR’s technological determinism—many applications for new biological products fail. This includes technologies that, like CRISPR, ignite great promise among scientists and the public alike. Non-CRISPR-based gene therapies had been repeatedly rejected by the FDA for decades, for example, despite their immense promise in treating genetic disease.<sup>16</sup> The FDA has also continuously rejected applications for stem-cell therapies, despite the public’s decades-long fascination with them.<sup>17</sup> And after being the subject of the 2006 Nobel Prize in Physiology and Medicine, the FDA only recently approved the first therapy making use of RNA interference (RNAi) technology.<sup>18</sup> If the FDA is anything, it is the legal embodiment of the precautionary principle.

It is true, of course, that the FDA’s jurisdiction, while broad, extends only to assessments of therapies’ safety or efficacy. The agency does not, at least formally, consider the public-health impacts of such technologies, how they will be economically distributed, or whether they will be *used* ethically once approved<sup>19</sup>—all risks that a precautionary approach may well avoid. But this does not mean that a robust new layer of oversight is needed to put such precautions into practice. First, while the FDA has little power to prevent the introduction of novel technologies *solely* on public-health, economic, or ethical grounds, the reality is that such concerns frequently overlap, in practice, with safety and efficacy issues, the agency’s core competence.<sup>19</sup> The FDA has significant power, for example, to narrow a therapy’s approved medical indication—an important touchstone, in many instances, for whether insurance reimbursement is available.<sup>20</sup> And any new technology that poses public-health risks writ large are also likely to pose safety and efficacy risks too.<sup>19</sup> Second, despite limits to its authority, the FDA has nonetheless expressed interest in engaging in dialogue

concerning the effects of its decisions on public-health and distributional consequences.<sup>19</sup> Moving such authority away from agencies such as the FDA in the name of additional oversight may cut such critical dialogue short. And third, the FDA's technical expertise in new biotechnologies puts it in a supreme position to address many of the risks sought to be guarded against with the precautionary principle. Commenting on the FDA's expertise in this area in the aftermath of the He experiments, Charo noted that the agency had "the most obvious opportunities to shape the direction of research and applications ... can impose the most stringent standards of proof for safety, multigenerational stability, and efficacy of edits before even considering an application for beginning clinical trials; [and] can also limit review to edits of genomic sites associated with particularly onerous medical conditions."<sup>21</sup> Whatever their shortcomings, regulatory agencies, such as the FDA and the USDA, and others outside the United States, are ultimately responsible for putting the precautionary principle into legal practice.

### Tort Law and Deterrence

Beyond regulatory agencies, there is tort law—typically, the civil, monetary redress of harms caused by the negligence of others. This includes products liability actions, cases concerned with defective products or inadequate services that harm their users physically or economically. As applied to CRISPR, this means that those injured by the negligent use of the technology could, at least in the United States, sue to redress their harms.

At first blush, the tort regime seems to run orthogonal to the precautionary principle. Tort redress appears to be *post hoc* rather than precautionary. And this is precisely the concern expressed by many bioethicists about the nature CRISPR as a technology. Because CRISPR is cheap, easy, and readily available, its risks are not well contained in the way that risks from larger more institutional projects are. Mitigating harms *after* widespread deployment of a new technology is famously inefficient.<sup>22</sup>

But tort law is grounded in *deterrence* not merely *distribution*.<sup>23</sup> Tort liability, done well, should strike enough fear into the hearts of a technology's users to ensure that the technology is used safely, ethically, and responsibly.<sup>24</sup> In that sense, a well-oiled tort regime is well aligned with the precautionary principle: it seeks to deter, absent sufficient precautions, unsafe uses of a technology. And indeed, tort judgments have changed numerous technological and medical practices heralded in the bioethics canon.<sup>25</sup> Further, one of the criticisms of the tort regime is that it may, as a deterrent, go too far, chilling the adoption of beneficial biotechnologies simply for fear of threat from suit.

The tort regime has more to commend to it than simply this fear. Aside from punitive monetary judgments, tort law also contemplates injunctions—a court order outright forbidding a particular practice because it has found be to harmful or likely to be harmful. More simply put, the tort regime allows judges—after weighing the appropriate evidence—to bar a certain activity from occurring because it is unethical, unsafe, or otherwise harmful. Oftentimes, these injunctions—while only applying the parties in the litigation—compel others to follow suit. This is not altogether different from panels of experts weighing in on the import of a new technology, as they are currently being collected for CRISPR.<sup>26</sup> Some injunctions even operate *before* a trial has been completed—preliminary injunctions—that, above all else, seek to "preserve the *status quo*."<sup>27</sup> Like premarket approvals in the regulatory context, preliminary injunctions for torts can work as precautions.

### Patents and Ethical Licenses

Similar to tort judgments, patents—at least, ideally—can be harnessed to drive the precautionary principle as well. As the axiom goes, patents are the right to exclude, that is, *prevent*: they allow their owners to prohibit others from practicing the claimed technology without prior permission. That is not a by-product of patent law; they are, contrary to much misconception, patents' *only* power. The power can be an extraordinarily economically powerful one—one of the explanations for the viral interest in patents covering CRISPR. Famously, the University of California and the Broad Institute fought over foundation aspects of the CRISPR-Cas9 patents precisely because of their perceived economic returns.<sup>28</sup> The winner—still not entirely clear—will possess immense power, both legal and economic, to prohibit others from practicing the technology.

Those seeking to use patented technology may obtain permission from a patent holder to do so; this constitutes a license. Licenses, although permissive by nature, may be used to restrict others in limited ways, such as performing unethical research. And licenses, especially for biotechnology, are often global in nature. This is precisely the Broad Institute's practice with respect to its CRISPR patents. It prohibits licensees from using its technology in ways that it has deemed unethical, namely to conduct human germline editing experiments and to conduct certain research on tobacco.<sup>29</sup> While such licenses can last only as long as the patent is valid, this "ethical licensing" approach is ultimately a form of the precautionary principle: a legal restriction on uses that are deemed dangerous or societally harmful.

Aside from the cooperative nature of licenses, there is also the threat of patent infringement suits against

recalcitrant users—the threat of suing those who use the technology unethically. Often, such suits come with injunctions prohibiting the patented use in question—further serving the model of prohibiting unethical users before they are widely spread. This is, in fact, the model proposed by Kevin Esvelt to rein in gene drive, an application of CRISPR to “drive” certain alleles through populations that have sparked heated ethical concerns.<sup>30</sup> The threat of infringement—the threat of halting proponents of unethical uses of the technology into a courtroom—is also a legal demonstration of the precautionary principle. In the words of Antonio Regalado, such approaches are meant to “stop gene spills *before* they happen.”<sup>30</sup>

### Funding Agencies and Review Boards

Prior to the commercialization of technologies—when they are typically still basic research—government funding agencies also play a critical *legal* role in furthering the precautionary principle. Several public agencies—the National Institutes of Health, in particular—require researchers to seek prior committee approval before beginning their experiments. Such committee approvals—the alphabet-soup review boards—typically center on the safety and ethical safeguards of experiments. This includes, of course, Institutional Review Boards to conduct “ethical reviews” of any proposed experiments<sup>31</sup>; Institutional Biosafety Committees to consider, in addition to its safety mandate, “ethical principles” with which experiments are to be conducted<sup>32</sup>; and, for animal research, an Institutional Animal Care and Use Committee similarly to review the “ethical necessity” of engaging in such research.<sup>33</sup> Failing reviews of such committees generally prohibit such experiments from being carried out—at least in their described form—by applicants. There are similar funding schemes—with expert oversight—in Europe and elsewhere.

Here, too, these reviews function much like a deliberative body of experts—and in most cases are, indeed, convened *by* experts—to pass on the ethical ambit of such experiments prior to them being conducted. In the context of CRISPR, CRISPR experiments can—and do—undergo such reviews, with several CRISPR experiments stopped because of ethical and safety concerns.<sup>34</sup> If the goal of the precautionary principle is, indeed, precaution—rather than outright moratorium—the ongoing oversight of such committees at least provides a forum for such a principle to operate.

### Politics and Prohibition

Lastly, there is always local politics—that is, small-*D* democratic participation in state and municipal govern-

ment to prohibit certain activities from occurring in constituents’ backyards. Such daggers have famously been wielded to prohibit certain research from being conducted, ostensibly on ethical grounds—notably, the Cambridge City Council’s 1976 six-month moratorium on research involving recombinant DNA, after significant and contentious public hearings.<sup>35</sup> Perhaps less well known is that similar restrictions on research were also enacted at the state level—New York and Maryland—as well as the towns of Princeton, Amherst, Waltham, Berkeley, and Emeryville.<sup>35</sup>

Local participation in such governance—lauded by notable bioethicists—has found its way, again, to police certain uses of CRISPR. Efforts to use one form of CRISPR, “gene drive,” to control the pest species, like the white-footed deer mouse and vector mosquitoes, have come under significant local scrutiny specifically in Martha’s Vineyard, Massachusetts, and Key West, Florida.<sup>36</sup> In those cases, public discomfort with such uses is one of the principal reasons they have not been widely deployed. In a similar although much more controversial vein, democratic action—such as the 2015 anti-GMO protests in France—have been used essentially to prevent the market introduction of novel biotechnologies. In this sense, the *legal* power of local government is a true democratic implementation of the precautionary principle. Further, as with the case in France, local democratic action can lead to national policy to ban or otherwise make unattractive the use of contentious technologies. Whether such interventions are ultimately scientifically (or ethically) sound remains to be seen. But such measures prove that the precautionary principle is alive and well in local legislation.

### Conclusion

Contrary to the notion that widespread use of CRISPR is *fait accompli* and thus not subject to meaningful ethics reviews that embody the precautionary principle, a diverse and broad fabric of legal regimes, mostly domestic but some international, has the capacity to slow, and in some cases prevent, the introduction of CRISPR technologies without certain precautions. Bioethicists and policy makers who are otherwise interested in conducting ethical assessments of CRISPR “before it’s too late” would do well to consider these in further detail. This is not to say that such regimes are perfectly precautionary—far from it. But even if they only imperfectly capture ethical concerns over the adoption of the technology, they go a long way in policing some of the most serious “rogue” applications.<sup>21</sup> Like CRISPR itself, the law has a great many applications; its capacity is limited only to that which we can feasibly imagine.

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