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Christi Guerrini

Margaret Curnette

Jacob S. Sherkow
*New York Law School*, jacob.sherkow@nyls.edu

Christopher Scott

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# The rise of the ethical license

Christi J Guerrini, Margaret A Curnutte, Jacob S Sherkow & Christopher T Scott

**The Broad Institute's recent licensing of its gene editing patent portfolio demonstrates how licenses can be used to restrict controversial applications of emerging technologies while society deliberates their implications.**

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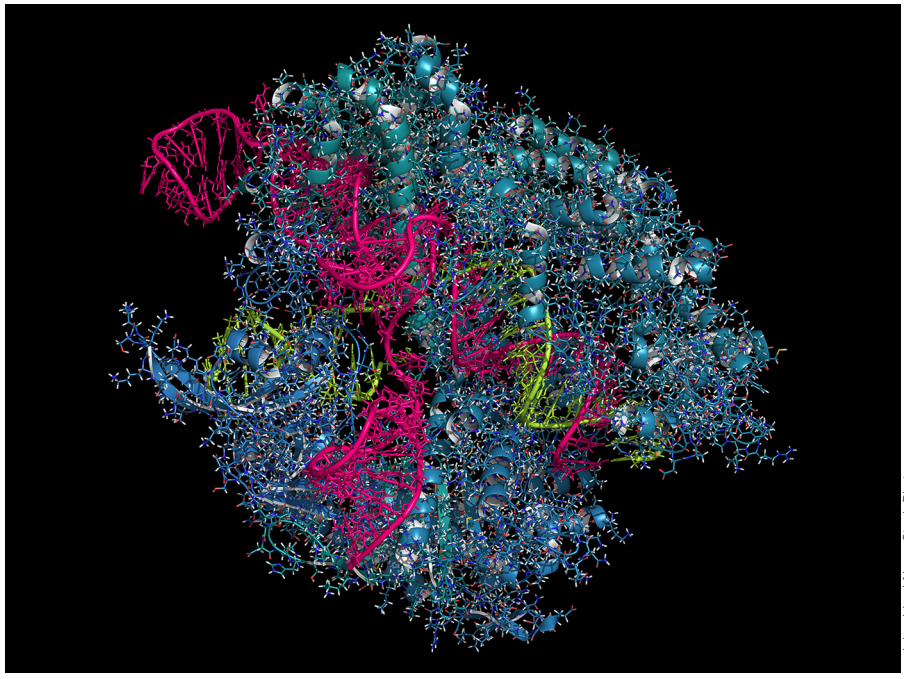
In September 2016, the Broad Institute announced that it had licensed its patents for the groundbreaking CRISPR technology on terms intended to benefit a party not at the negotiating table: the public. As broader policy positions on gene editing technologies emerge, this agreement illustrates how licensing can serve as a tool to limit potentially controversial uses of patented technologies as they enter the marketplace. Here, we discuss some of the advantages and barriers to using this approach.

CRISPR (bacterial clustered, regularly interspaced, short palindromic repeats) is a gene editing tool that can disable, replace, or insert specific nucleotides in a genome, and the Broad owns what are considered to be the foundational patents on this technology[1]. Although the University of California has launched a vigorous challenge to the Broad's patent rights[2], since 2014 the Broad has been offering licenses to its CRISPR patent portfolio for research and commercial purposes. A number of licensees are moving forward with applications of the technology while other researchers are developing their own intellectual property in unclaimed uses of CRISPR[1]. In 2015, over 100 patent applications on CRISPR technology were pending[3]. Meanwhile, companies using first-generation gene editing technologies like zinc finger nucleases and TALENs (transcription activator–like effector nucleases) are on the verge of bringing new products to market[4].

As intellectual property rights in this technological space have multiplied, so, too, have ethical and social concerns about CRISPR's potential applications. Those applications include altering human somatic cells, which make up organs, blood, and skin, and human germ cells, which include sperm and egg cells. While few would object to editing genes to cure devastating diseases, CRISPR technology has the potential to alter the health, behavior, and appearance of every life form. Some fear that in unscrupulous hands, CRISPR might one day be used to create humans genetically enhanced for intelligence, beauty, and strength. These fears are multiplied in cases of germline editing, where changes are passed on to future generations[5]. Worries about germline applications are heightened by CRISPR's ability to power so-called 'gene drives' that alter normal patterns of inheritance such that engineered genes are always passed on to future generations[6]. This technology can be used, for example, to engineer the extinction of an organism.



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The potential applications of CRISPR to alter future generations in unpredictable and unacceptable ways led a group of scientists and ethicists—including some inventors of the technology—to strongly discourage clinical applications of human germline editing until the risks and benefits have been thoroughly examined[7,8]. Nonetheless, Chinese researchers have moved ahead with experiments having clear therapeutic goals. Using CRISPR in nonviable human embryos, one research team knocked out the human gene *HBB*, while another introduced *CCR5*, an HIV-resistance allele[9,10].

As the United States, China, and the United Kingdom coordinate policy responses to these issues[11], an international consensus on the use of CRISPR technologies is slowly emerging: controlled and transparent basic research should continue, but clinical applications

*Christi J. Guerrini, Margaret A. Curnutte and Christopher T. Scott are at the Center for Medical Ethics and Health Policy, Baylor College of Medicine, Houston, Texas, USA, and Jacob S. Sherkow is at the Innovation Center for Law and Technology, New York Law School, New York, New York, USA.*
*e-mail: guerrini@bcm.edu*

should be banned until relevant safety, efficacy, and ethical issues have been resolved. Meanwhile, a National Academy of Sciences committee is gathering information for the purpose of guiding US policy (http://nationalacademies.org/gene-editing/index.htm).

Given the enormous challenges of developing practice and legal standards that appropriately balance the interests of individuals, society, and future generations, it is no surprise that researchers and policy makers are approaching these issues cautiously and with great care. The slow pace of social and ethical reckoning, however, means that until stakeholders fully process CRISPR's potential, it is free to be used—and abused—with few legal constraints.

Notably, the use of patent licensing to limit applications has not yet entered the national or international policy conversation. Yet, the Broad's recent license of its CRISPR patent portfolio to Monsanto exemplifies a potentially powerful new solution to this temporal problem: using patent licenses to restrict socially controversial applications of a technology. During a patent's term, one may not practice an invention claimed in the patent without a license from the patent holder. By prohibiting uses the patent holder deems unethical, a patent license can function as a tool of private governance. And because the patent right is limited in duration, this approach has a built-in expiration date far enough in the future to provide policy makers and broader society more time to move deliberatively toward policy solutions.

According to the license agreed upon by the Broad and Monsanto, Monsanto may use the Broad's CRISPR patents for agricultural purposes, such as the production of seeds that resist drought or present improved nutritional profiles. In conducting this research, however, Monsanto may not engage in three activities that the Broad identified as raising ethical and safety concerns.

The prohibited activities are: (i) performing gene drives that spread altered genes quickly through populations, which can alter ecosystems; (ii) creating sterile 'terminator' seeds, which would impose a serious financial burden on farmers who would be forced to buy them each year; and (iii) conducting research directed to the commercialization of tobacco products, which might increase the public health burden of smoking[12].

Two years earlier, and with much less fanfare, the Broad exclusively licensed its CRISPR patents to Editas Medicine for human disease prevention and therapeutic purposes, and that license also includes socially beneficial restrictions. Specifically, Editas agreed not to use the technology to modify human germ cells or embryos for any purpose or to modify animal cells for the creation or commercialization of organs suitable for transplantation into humans[13].

Using patent licenses to pause worrisome applications of emerging biotechnologies has several advantages over formal policy making and standard setting. First, this private solution is more efficient than formal policy making because it does not require consensus among many stakeholders but only the commitment of a single entity: the patent owner. And because the patent owner is frequently the original developer of the technology, it can be in the best position to anticipate controversial applications. Second, unlike most professional guidelines, licensing restrictions are enforceable in court, and a licensor may include penalties in the license for violating those restrictions. Third, unlike laws and government regulations, which are typically blunt policy instruments, patent licenses can be tailored to the specific circumstances of their parties, who are motivated to ensure that any use restrictions are appropriately narrow. Fourth, licensing restrictions are the products of negotiation among affected parties and therefore should be associated with greater buy-in than federal statutes and institutional standards dictated, sometimes, by lay politics.

Despite these advantages, we recognize that there are substantial barriers to using patent licensing as a mechanism for curbing controversial technological applications. For one, adding ethically motivated use restrictions to licenses decreases the value of those licenses, since those who agree to such restrictions generally receive a discount to bear the additional burden. An institution with significant financial interests at stake in its patents may be unwilling to weaken the market for those patents by playing ethicist.

More broadly, however, patent owners may be torn about policing socially beneficial limits on their technologies since doing so requires making—and assuming responsibility for—difficult assessments of the implications for local, national, and global communities. For example, how should a licensor consider the ethics of technologies likely to affect the sequencing of native peoples who might oppose such research?

Although evaluations like these are imprecise, with respect to applications like germline editing, it is easier to conclude that concerns associated with those applications currently trump their potential benefits. In such instances, the social benefits associated with voluntarily engaging in ethical licensing will spill over beyond those who merely comply with such licenses. These spillover effects may include, for example, increased faith in scientific self-regulation and participation in research. Voluntarily restricting applications can also generate goodwill among the licensing parties and promote institutional leadership that might translate to new, collaborative partnerships. Presumably, at least some of these public and private benefits have prompted others to place patent-facilitated limits on controversial innovations. These include Massachusetts Institute of Technology scientist Kevin Esvelt's plan to enforce gene drive patents against academics who use the technology but do not disclose their research plans and attendant safety and ethical issues[14]. Similarly, these benefits likely dovetail with humanitarian instincts to license technologies in less-than-profit-maximizing ways, such as requiring the development and distribution of technologies to underserved populations[15].

For other technologies, however, there may be substantial uncertainty regarding which patent licensing restrictions will maximize social welfare—or at least prevent social harm. Technologies like CRISPR that implicate large numbers of disparate social interests may sound an alarm that drowns clear calls to action. As a result, some licensors may forego pursuing socially beneficial licensing. Alternatively, they may adopt license terms that are inconsistent or even mutually defeating. Taking the concern to its extreme, patent owners may even reject coordination and elect instead to separately pursue lucrative applications that are widely opposed as unethical, such as licensing CRISPR technologies for germline engineering.

These problems are not intractable, however. CRISPR stakeholders agree on the need for a coordinated response to the scientific, ethical, legal, social, and governance issues associated with human gene editing, and several major efforts are underway to develop relevant practices and policies. We believe that these efforts should include explicit consideration of patent licensing as a tool of privately driven governance, which thus far has been absent from the conversation. Further, as to any restrictions on CRISPR specifically, we urge the consideration of whether such restrictions should be incorporated in patent licenses.

In the meantime, and looking beyond CRISPR to other controversial biotechnologies such as non-invasive prenatal testing, we urge innovators to follow the Broad's lead and adopt the practice of using patent licenses to restrict socially harmful applications of their technologies. Innovators should be encouraged to identify and address such instances in their patent licenses.

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For the sake of transparency and to facilitate further socially beneficial licensing, innovators should also be encouraged to follow the Broad's example of publicly disclosing the terms of and reasoning behind any license restriction policies they have adopted[16]. Where licensing includes confidential business information, the public does not need to know the financial details of a licensing deal. But if socially beneficial licensing is truly for the public, the patent holder should inform the public of any terms of use that are adopted on its behalf.

As a mechanism for addressing controversial applications of biotechnologies like CRISPR, we do not suggest that private agreements are preferable to, or should be used to the exclusion of, policy making or professional standards setting. We view these two systems—public regulation and private governance—as complements to each other. We hope simply to highlight the advantages of private agreements that have not yet been fully exploited. Most likely, some combination of public and private efforts will be necessary to ensure that CRISPR's promise of public welfare is fully realized.

**COMPETING FINANCIAL INTERESTS**
The authors declare no competing financial interests.

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