



Ethics, Patents and Genome Editing: A Critical Assessment of Three Options of Technology Governance

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OPEN ACCESS

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Specialty section:

This article was submitted to
Politics of Technology,
a section of the journal
Frontiers in Political Science

Received: 27 June 2021

Accepted: 07 September 2021

Published: 21 September 2021

Citation:

Feeney O, Cockbain J and Sterckx S
(2021) Ethics, Patents and Genome
Editing: A Critical Assessment of Three
Options of Technology Governance.
Front. Polit. Sci. 3:731505.
doi: 10.3389/fpos.2021.731505

Current methods of genome editing have been steadily realising the once remote possibilities of making effective and realistic genetic changes to humans, animals and plants. To underpin this, only 6 years passed between Charpentier and Doudna’s 2012 CRISPR-Cas9 paper and the first confirmed (more or less) case of gene-edited humans. While the traditional legislative and regulatory approach of governments and international bodies is evolving, there is still considerable divergence, unevenness and lack of clarity. However, alongside the technical progress, innovation has also been taking place in terms of ethical guidance from the field of patenting. The rise of so-called “ethical licensing” is one such innovation, where patent holders’ control over genome editing techniques, such as CRISPR, creates a form of private governance over possible uses of gene-editing through ethical constraints built into their licensing agreements. While there are some immediately apparent advantages (epistemic, speed, flexibility, global reach, court enforced), this route seems problematic for, at least, three important reasons: 1) lack of democratic legitimacy/procedural justice, 2) voluntariness, wider/global coordination, and sustainability/stability challenges and 3) potential motivational effects/problems. Unless these three concerns are addressed, it is not clear if this route is an improvement on the longer, slower traditional regulatory route (despite the aforementioned problems). Some of these concerns seem potentially addressed by another emerging patent-based approach. Parthasarathy proposes government-driven regulation using the patent system, which, she argues, has more transparency and legitimacy than the ethical licensing approach. This proposal includes the formation of an advisory committee that would guide this government-driven approach in terms of deciding when to exert control over gene editing patents. There seem to be some apparent advantages with this approach (over traditional regulation and over the ethical licensing approach mentioned above—speed and stability being central, as well as increased democratic legitimacy). However, problems also arise—such as a “half-way house” of global democratic legitimacy that may not be legitimate enough whilst still compromising speed of decision-making under the “ethical licensing” approach). This paper seeks to highlight the various advantages and disadvantages of the three main regulatory options—traditional regulation, ethical licensing and Parthasarathy’s approach—before suggesting an important, yet realistically achievable, amendment of TRIPS and an alternative proposal of a WTO ethics advisory committee.

Keywords: genome editing, CRISPR, ethical licensing, patents, governance, TRIPS

INTRODUCTION

Compared to previous techniques of genetic intervention, CRISPR (clustered regularly interspaced short palindromic repeats), and in particular CRISPR-Cas9, has been steadily changing the discourse on gene modification from one of future possibilities to that of emerging realities. There have been a number of promising developments of the CRISPR tools in research (e.g., research on heritable disease (DMD) and infectious disease (HIV); corrections of genetic bases to some heart defects, and to beta thalassaemia). Throughout this time, there have also been developments that have caused concern (e.g., 2015 embryo gene-editing experiments) and, in November 2018, some outrage. To underscore the revolutionary advances in technical capacity, only 6 years passed between Charpentier and Doudna's 2012 paper outlining the CRISPR-Cas9 technique, and He Jiankui's case of reproductive human gene-editing (Jinek et al., 2012; Cyranoski and Ledford, 2018). He's gene-editing of twin girls was an attempt to confer immunity to HIV. This case has been significant not only for its extension of gene-editing to humans, but also due to the ethical and legal guidelines ignored in the process (Feeney, 2019).

While the traditional legislative and regulatory approach of governments and international bodies is evolving (Baylis et al., 2020), there is still considerable divergence, unevenness and lack of clarity (Nordberg et al., 2020). Nevertheless, besides in technical progress, innovation has also been taking place in the proposals of new forms of ethical guidance and regulation for gene-editing—from the field of patenting. Guerrini et al. (2017) have noted the rise of so-called 'ethical licensing' where institutions, researchers and companies have used their patent control over CRISPR techniques (especially in the case of the foundational patents) to create an emerging form of private governance over some uses of gene-editing. Unlike the partial, ineffective patchwork of uncoordinated and outdated regulatory and legislative systems across different jurisdictions at the international level, the patent system has global scope through the 1994 TRIPS Agreement (Feeney et al., 2018). While there are some immediately apparent advantages (epistemic, speed, flexibility, global reach, and court enforcement), this route seems problematic for, at least, three important reasons: 1) lack of democratic legitimacy/procedural justice, 2) voluntariness, wider/global coordination, and sustainability/stability challenges and 3) potential motivational effects/problems. Unless at least these three concerns are addressed, it is not clear if this route is an improvement on the longer, slower traditional regulatory route.

Some of these concerns seem potentially to be addressed by another emerging patent-based approach. Parthasarathy (2018) proposes government-driven regulation using the patent system, which, she argues, has more transparency and legitimacy than the ethical licensing approach. Her proposal includes the formation of an advisory committee that would guide this government-driven approach in terms of deciding when to exert control over gene editing patents. There seem to be some apparent advantages with this approach over the traditional regulation and ethical licensing approaches—speed and stability being central, as well as increased democratic legitimacy. However, problems also arise—such as a

“half-way house” of global democratic legitimacy that may not be legitimate enough whilst still compromising the speed of decision-making under the ethical licensing approach.

In both patent-based suggestions, it must also be examined whether, or to what degree, this focus lessens the urgency for, or interferes with, the more robust, regulatory/legislative approach. This paper seeks to highlight the various advantages and disadvantages of the three main options—traditional regulation, ethical licensing and Parthasarathy's approach. We will argue that ethical licensing, if it occurs and the objectives are just and ethical, is to be welcomed. However, this method itself cannot be sufficient as it would just as easily permit unethical objectives. Even if the objectives were ethical, stability and democratic accountability would still be problematic. A prominent concern would also be that this route would slow down the urgency for seeking more traditional regulatory options, whilst at the same time increasing the power of biotechnological companies. Finally, we suggest an additional proposal, entailing an important, but still realistically achievable, amendment of TRIPS and an alternative proposal of a WTO ethics advisory committee that can, and should, be put in place to guide signatory countries worldwide. Throughout, we do not promote this or any patent-related route as the sole, or necessarily optimal, approach to regulating new technologies, such as genome editing, but rather that it may usefully be part of a range of responses, including working alongside forms of traditional regulation. If and where the latter is insufficient, the patent-based route, including our proposal, can be considered beneficial additions to the field.

Background—Technological Progress and Regulatory Inertia?

In the October 2010 issue of *Scientific American*, an article by Stephen S. Hall entitled “Revolution Postponed” outlined a number of areas that had not progressed as speedily as was predicted during the heady days of the Human Genome Project (Hall, 2010). While such arguments are not particularly accurate or fair—for instance advance in basic research has been immense—there is no doubt as to their accuracy for the decade that immediately followed that article. With major milestones occurring in the 2015 case of CRISPR gene-editing of nonviable human embryos and the 2017 case of the CRISPR correction of the genetic basis of the congenital heart condition hypertrophic cardiomyopathy, only 6 years passed between Charpentier and Doudna's seminal 2012 paper outlining the CRISPR-Cas9 technique, and the first confirmed case of gene-edited humans (Jinek et al., 2012; Cyranoski and Ledford, 2018). In 2018, Jiankui He claimed to have performed germ-line reproductive gene-editing of twin girls—Lulu and Nana—by inserting a variant of the CCR5 gene in an attempt to confer immunity to the human immunodeficiency virus (this was followed with a later claim of a third gene-edited child). Increasing the speed of technical advance puts pressure on ethics and law to catch up.

However, in this case, it was not just areas of ongoing ethical disagreement and still forming ethical values and principles that gave rise to moral unease. It was also the discarding of well-established values and principles that gave rise to moral outrage. From safety concerns and lack of medical necessity to charges of eugenics, He's case highlighted that we no longer have the silver

lining of slow technical progress for further moral reflection before potentially problematic genetic interventions are attempted (Feeney, 2019). While the genome editing techniques of Zinc-finger nucleases (ZFNs) and transcription activator-like effector nucleases (TALENs) already had potential, CRISPR has revolutionised what was usually termed genetic engineering by making it cheaper, more accurate and more efficient. This is not to suggest that CRISPR-Cas9 is the only gene-editing technique in use. ZFNs and TALENs are still considered as major contemporary forms of genome editing technologies (Gaj et al., 2013; Li et al., 2020). Nor, does “more” efficient and accurate mean efficient and accurate (a line is straight or it is not—more straight suggests still not straight).

Nevertheless, the “CRISPR Revolution” has also meant that the ethical discussions over the previous decades, on what changes, if any, we can morally make to humans is less one of future speculation and more one of imminent or current application. Moving beyond well-established clinical research ethics, new ethical issues arise, for instance, in arguments that favour somatic, as opposed to germline, interventions; the latter are arguably problematic insofar as they can affect future generations in unpredictable and irreversible ways (Ranisch and Ehni, 2020). Other concerns include the risk of the use or misuse of the technology for enhancement purposes (WHO, 2021) as well as issues of social justice between those who have their genomes edited, and the rest (Baylis, 2019). Since the Chinese case, claims by a Russian biochemist have raised the prospect of more such interventions in the future (Kravchenko, 2019). Others will surely follow.

While it appears that He was severely sanctioned by the Chinese authorities (Cyranoski, 2020), his case exposed the lack of a clear and coherent international legal or regulatory structure. In fact, the only international ethical instrument with legal force in relation to gene-editing is the Convention on Human Rights and Biomedicine (the Oviedo Convention). However, this only covers countries party to the Council of Europe, and then only those who sign and ratify it. Moreover, this Convention entered into force in 1999, suggesting that there are, at least some, aspects to it that are long out of date, including any consideration of CRISPR or other contemporary genome editing techniques. The Council of Europe’s Committee on Bioethics (DH-BIO) recent examination of Article 13 of the Oviedo Convention in light of gene editing technologies did not embark upon a wider exploration of the ethical and legal issues arising in recent years, confining itself to relatively minor adjustments and clarifications¹. It is not clear that minor revisions will be sufficient. This is not unique to the Oviedo Convention. As

Parthasarathy (2018) notes “when it comes to editing genes in humans and other organisms, the United States and the United Kingdom—along with many other countries—rely on laws and policies that cover existing genetic engineering technologies”. Nordberg et al. (2020) highlight how the current legislative and regulatory framework in Europe incorporates some general principles advanced by the United Nations Educational, Scientific and Cultural Organization (UNESCO). While this may constitute some degree of soft law applicable in the EU arena, Nordberg et al. highlight that some considerable divergence still exists between national regulations and well as lack of clarity regarding the available legal tools.

The lack of clarity on the international level with regarding to the legislative and regulatory options regarding human genome editing is compounded by a lack of empirical work (or lack of rigour in such work) in contemporary discussions. Françoise Baylis et al. (2020) highlight a failure of such discussions to properly acknowledge and accurately portray the existing legislation, regulations, and guidelines on research in human genome editing. Indeed, according to the review of some of the literature by Baylis et al., the expected Chinese reaction to reproductive human genome editing could have ranged from permissive regulation to outright prohibition. However, as the authors observe, there is some degree of consensus in the global setting. With regard to emerging policy on heritable human genome editing, Baylis et al. (2020) found a “broad prevalent agreement” in the international setting which suggests “that development of international consensus on heritable human genome editing is conceivable”. Unsurprisingly, the rough consensus is prohibition. Nevertheless, this international consensus may soon be moving in a new direction that is reflected in a recent Report written largely in response to the gene-edited twins in China. The International Commission on the Clinical Use of Human Germline Genome Editing’s 2020 Heritable Human Genome Editing Report concluded that implanting edited embryos to establish a pregnancy was not justifiable, at this time. Research into heritable human genome editing could proceed, subject to stringent guidelines for carefully progressing toward clinical research and clinical application, such as on monogenetic disorders. In this respect, the Report seeks to offer a translational pathway for the approval of human heritable genome editing in limited cases, where such stringent criteria are met (e.g. where no developmental abnormalities are detected). Furthermore, this could feed into the appropriate WHO governance and monitoring mechanisms for heritable and non-heritable genome editing in clinical use and research in humans. Amongst other things, this would give rise to increasing complexity for legislation and regulation in the different countries—including those that may currently have some form of rough consensus. Outright prohibition is—in one sense—easy: you ban it. But permitting some uses, while temporarily or permanently banning others is not so straightforward and may also break the aforementioned consensus. Noting germline genome editing that is not for reproductive purposes, Baylis et al. (2020) observed a greater international divergence than in the case of its heritable version. As the technology becomes more established, it is plausible, at

¹The limited revisions include clarifications “on the terms “preventive, diagnostic and therapeutic” and to avoid misinterpretation of the applicability of this provision to “research”. Council of Europe news page: Genome editing technologies: some clarifications but no revision of the Oviedo Convention, June 7, 2021: <https://www.coe.int/en/web/human-rights-rule-of-law/-/genome-editing-technologies-some-clarifications-but-no-revision-of-the-oviedo-convention> [accessed 22.08.21]. It seems highly implausible to suggest that these few revisions address all the significant advances, and associated ethical and legal implications, over the last decades.

least, to suggest that some of the initial prohibition standpoints may also soften in the case of heritable changes.

The greater the divergence in international governance (whether in relation to germline or potentially heritable editing), the greater is the risk of unscrupulous actors, companies or indeed states moving genome editing operations to other locations where there are no prohibitions or other restrictions. There may be countries or regions that, while agreeing in principle with a cautious WHO global governance and monitoring mechanism, may not have the local regulatory infrastructure to police rogue actors. Such countries may have legislation in place but no enforcement capability. Similarly, other places may not have the resources to divert to spending time on either legislating on or regulating human genome technologies, let alone enforcing them (Baylis et al., 2020). Other states may be under severe geo-political pressures that creates space for rogue actors to operate. A clinic in Ukraine is purportedly planning to sell CRISPR enhancements (Knoepfler 2021). It is more likely that the Ukrainian government is preoccupied with its conflict with Russia and Russian supporting separatists, than it is eagerly supporting a CRISPR “wild west” in the eastern edge of Europe. It is also not beyond the realms of probability that countries that continue to be at odds with a “western consensus” in terms of military expansionism or vaccine development outside of basic ethical standards, may take entirely regional—not “global”—approaches to human genome governance. A new cold war may arise in the development of human genome editing technologies—a not unlikely prospect given the potential military applications of the technology. “Ethics dumping” may not only be a risk for countries who are unprepared in terms of human genome editing policy—it may be a deliberate political decision (Schroeder et al., 2019).

Appropriately robust and well-balanced international legislation will likely be slow in its development, and subject to persistent moral disagreement (Nordberg et al., 2020). The fact that the Oviedo Convention, now two decades old, is the only international legally binding form of legislation, and applies only within part of Europe, is not exactly confidence inspiring.² It is also not clear that old regional/geo-political rivalries will not re-emerge in the heritable, or non-heritable, human genome editing context. Moreover, this may not be confined to monogenic disorders, but cases of therapy vs. enhancement, or other cosmetic treatments, as suggested by the plans of the Ukrainian clinic. The international legislative-regulatory route is far from the finish line, but it should not be abandoned. However, the question of whether other horses should enter the race must also be considered.

A Novel Form of Technology Governance

Legislation to allow governments or international bodies to constrain performance of gene-editing, is not the only way to regulate genome editing. Innovations in the field of patents are

giving rise to new forms of (potential) ethical guidance and regulation in gene-editing. The original CRISPR-Cas9 patents were taken out by two groups: the University of California, Berkeley and University of Vienna group of Jennifer Doudna and Emmanuelle Charpentier regarding its use in general, and the MIT/Harvard/Broad Institute group of Feng Zhang regarding its use on eukaryotes in particular, including plants and animals (Feeney et al., 2018). These two groups, and various sub-groups, are issuing licences for CRISPR-Cas9 to various researchers, institutions, and companies across the globe. These licences are crucial as CRISPR is a tool that is fundamental to many areas of research and applications in humans, non-human animals, plants and microorganisms.³ The technique is used in—and essential to—a vast amount of gene-editing research and many of the patents on this technique are thereby foundational—without licences from the patent holders much work using CRISPR-Cas9 is open to litigation.⁴ Accordingly, this puts the patent holders in a significant position of power and control over CRISPR’s uses; a control that can be exerted via the constraints attached to the licences. In addition to the usual patent-related stipulations regarding payment of royalties and exclusivity or non-exclusivity, terms ostensibly based on ethical considerations are emerging in some of the CRISPR-Cas9 licences.

Guerrini et al. (2017) have noted the rise of “ethical licensing” where companies use their patent control over CRISPR techniques to require or forbid certain practices. This is done by having ethical constraints built into their licensing agreements. For instance, Broad’s CRISPR-Cas9 licences forbid the technique from being used in the editing of tobacco plants, with gene drives or for creating “terminator” seeds for agriculture (Broad Institute, 2017). Its licensing practices also forbids its use in human germline modification. All this, even though the local law may otherwise sanction it, or not prohibit it. Similarly, Kevin Esvelt’s (2018a) work on gene drives is focussed on balancing such an environmentally controversial technology by seeking wide community involvement, given the likely impact for all community members. Gene drives (where genetic alterations are spread through a population with increased rates of inheritance) are a good illustration of the future generations concerns in the case of human heritable genome editing. Examples of uses of gene drives include those in mosquitoes, fruit flies, and mice that are CRISPR’d to cause “desirable” changes to spread through a population at higher-than-normal rates of inheritance, in order to control the spread of disease or simply to control the animal population itself. This can have significant potential for widespread, and unanticipated, harms. In the spirit of ethical licensing, Esvelt sees the mobilisation of patent law to be faster than governmental bureaucracy and truly international in its reach (2018a: 30). Esvelt’s advocacy of gene drive technology developed as non-

²We are not here giving any indications regarding the acceptability, or not, of the Oviedo Convention itself; rather we are highlighting that (good or bad) it is still the only show in town with regulatory bite, insofar as it is ratified.

³We avoid here the many complications that the patent dispute has entailed for those institutions or researchers seeking licences. For more on this, see Feeney et al. 2018.

⁴Basic, non-profit, pure academic research may be exempt from paying royalties or even needing a licence at all. However, even amongst such groups, a fear of litigation is present.

profit, with the particular goal of preventing the profit motive from interfering with public trust, can be promoted with such a leveraging of intellectual property (Esvelt, 2018b).

On the face of it, ethical licensing is a potentially welcome initiative. In terms of regulation, rather than having nothing until we have a sufficient consensus, we have a smaller and faster form of ethical decision-making. Moreover, it is the scientists, institutions, and companies at the centre of the CRISPR-Cas9 discovery who are the patent holders. It could be argued that they are ideally placed to better appreciate the potential of their technology, as well as its possible positive and negative uses and, consequently, to devise better, more balanced regulations. There are at least four advantages that can be identified.

- **Epistemic**—politicians and policy makers are seldom scientific experts, and require numerous civil servants, and other advisors, to support their day-to-day work. They are also susceptible to lobbying and competing and conflicting pressures—e.g., technological safety versus economic benefits. While this does not suggest that those who invent or discover such technological innovations are immune to such conflicting pressures, there may be a better chance that they are better placed to make informed decisions regarding what is possible, realistic, genuinely dangerous, and also better able to balance such competing priorities.
- **Speed**—Regulation of technology can be slow at the best of times. In cases where a technology is controversial and novel, it can require the input of multiple stakeholders, rival interests, and mutually incompatible groups. The policymakers may include many such incompatible groups making compromise and deal-making an even slower process. Furthermore, the bureaucratic system in place will need to adopt the new policy and enact it, also taking time. On the other hand, control via the terms placed in patent licences can be—relatively speaking—almost immediate.
- **Flexibility**—This is an advantage similar to speed but still distinct in its own right. Moving at speed in terms of regulation and legislation can be one thing, but it may not include the ability to change course just as speedily if required. When new discoveries are made, or new information arises about an existing patented invention/discovery, there is no slow lag time for revising future licences when one is the patent holder. Even with existing licences, these might contain clauses permitting the patentee to modify the licence terms if new risks or benefits appear.
- **Global reach/court enforcement**—the traditional international regulatory landscape outlined above does not have any means of global enforcement, nor any firm picture of how one might operate. The only international example is the Oviedo Convention, which cannot even gain ratification from all the countries within the Council of Europe. By contrast, the patent landscape is court-enforced and well-established internationally.

Nevertheless, this route seems problematic for, at least, three important reasons, and unless these are addressed, it is not clear if

this route is a real improvement on the longer, slower traditional regulatory route.

Lack of Democratic Legitimacy/Procedural Justice

Firstly, and importantly, ethical licensing lacks the democratic legitimacy and broader consensus that underlies traditional systems of regulation. Of particular concern is the level of power that private governance approaches, such as ethical licensing, can concentrate in the hands of individuals who are not accountable to anyone, besides shareholders. In Feeney et al. (2018), one concern over patenting foundational technologies, such as CRISPR, was the power it afforded a small group to set the agenda for future research. Perhaps with noble intentions, the “ethical licensing” approach of Broad-Editas is a form of privatised morality—without discussion, debate, public involvement and democratic accountability—that forecloses ethical decision-making on a technology with a wide societal impact. Hilgartner (2018) highlights democratic choice and accountability as crucial in such cases which “shape the technological and social orders that govern our lives”. This, as Hilgartner notes, is a form of configuration power that is also evident in Esvelt’s proposal. While ethical licensing may be welcomed by some, such proposals—and the agenda-setting power they can have—makes “patent policy a matter of profound political importance” (Hilgartner, 2018). The 2013 U.S. Supreme Court ruling that human genes cannot be patented, invalidated key patent claims by Myriad Genetics on both the BRCA1 and BRCA2 genes. Prior to this, Myriad had effectively used its patent control to stop competitors from offering wider and cheaper clinical testing for determining cancer risk—doubtlessly resulting in late diagnosis, illness, unnecessary surgery and death. As Hilgartner notes, despite the ending of its monopoly, Myriad had already amassed an extensive and valuable database on BRCA variants, beyond what its new competitors had access to and therefore “Myriad’s configuration power partially outlived the patents that originally bestowed it”. Similarly, de Graeff et al. (2018) note, that while it is praiseworthy that Editas aims to pursue a socially responsible licensing approach, “leaving the determination of what is “socially responsible” to the sole discretion of the patentee, ethical licensing through private governance raises procedural justice concerns”. One response would be to reform the patent system (so far as possible in the non-ideal context) to reduce the level of exclusivity that patents can grant (Feeney et al., 2018; Feeney, 2019). This would constrain the potential for nefarious forms of agenda-setting or configuration power, while—to a greater extent—aligning itself with the socially positive goals of those involved in ethical licensing.

Voluntariness, Wider/Global Coordination and Sustainability/Stability Challenges

Secondly, there is the issue of wider coordination difficulties and likely disagreements between different private actors. This problem is centred on the voluntariness involved in the ethical licensing approach. Nor is the voluntary nature of ethical licensing something that can be easily circumvented—it is a defining characteristic of this approach. In the context of germline editing concerns trumping their current benefits, Guerrini et al. (2017) notes that:

[i]n 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 (23).

As advocates of virtue ethics will no doubt agree, legal compulsion alone cannot work as effectively without the cultivation of norms and motivations of people to want to comply with such legal requirements, without necessarily having to do so (Fives, 2013). However, while Arneson (2003) sees the potential of informal social norms over the “costly machinery of legal compulsion,” the problem is that norms tend “to sprout up like weeds” (2003: 145). Private governance priorities, if any, will depend on the individual patent holders and there is no reason to assume that all will follow the ethical licensing route or, even if they do, adopt the same scope of ethical licence restrictions. As outlined elsewhere (Feeney et al., 2018), much of the potential application of the currently dominant genome editing technique is built upon a common “foundational” technique of CRISPR-Cas9. This foundational technique is subject to the disputed, overlapping control of two groups (Doudna and Charpentier on one side over its application over DNA, *tout court*; Zhang on the other over its application on eukaryotic DNA (e.g. plant or animal DNA) and their respective patent claims (Feeney et al., 2018). This now infamous patent dispute has been held up as a pivotal example of how commercial interests can damage scientific collaborations (Sherkow, 2016). Even where “ethical licensing” has been seen to arise with actors in this dispute, there are issues over how long such ethical standpoints last—particularly for a wider group of people, over time in a private arena where profitability, for instance, is an alternative and competing value. As with many other areas, there is also the problematic issue of self-regulation by the patent holders over their own research and commercial activities (e.g. such as when cases of conflict of interest arise). While Contreras (2018) suggests that the option of voluntary solutions is being overly dismissed, the case of Myriad/BRCA alone highlights that any voluntary approach cannot be relied upon (Hilgartner 2018; Feeney, 2019).

Potential Motivational Effects/Problems.

In addition to the aforementioned concerns, there is an additional, less obvious issue that can problematise such a reliance on the ethical motivations arising in the private sphere. The sustainability of such voluntary non-profit (“other-regarding”) motivations in a for-profit (incentive-based) environment cannot be assumed. To illustrate, one can review the trend of patent control since the onset of modern genetic interventions, particularly in the USA. The revolutionary developments in recombinant DNA technology by Herbert W. Boyer and Stanley N. Cohen were of significant commercial potential and, patented by Stanford University, generated a sizable source of university funding (Cook-Deegan and Heaney, 2010). However, profit was not the primary goal of the Cohen-Boyer patents, and their licensing decisions largely reflected

public service ideals, preventing public harm, and increasing revenue for educational and research purposes (Feldman et al., 2007, 1798). Nevertheless, in the intervening years—which included the Bayh-Dole Act (1980)—Peter Lee notes that through “a long (and still ongoing) process of norm contestation, academic culture has become much more receptive to exclusive rights and the commercial exploitation of scientific knowledge” (Lee, 2013, 36). This issue is also something that may face similar ethical proposals in the leveraging of private sector motivations for a social or a public good. Norms can indeed sprout up like weeds, but how the local ecology is maintained may well influence the type of weed that is prevalent. This is concerned with the potential interplay between incentives and public-spirited motivations that can be seen with their attempted mutual accommodation in the wider Rawlsian literature.⁵ One key complexity that non-ideal theory recognises lies in stronger feasibility constraints than an ideal-theoretical approach to justice would acknowledge—such as what Rawls might consider “unreasonable levels of self-interest” (Farrelly, 2007; Farrelly, 2016). In economic theory, *Homo oeconomicus* is a term used to describe a view of persons as self-interested, rational utility maximisers. While real people (e.g. “pro ethical licensing” members of Broad) may not resemble this image, giving insufficient regard to what “reasonably” self-interested people are like in reality could render unworkable an overly ideal scheme of justice no matter how desirable it might otherwise be (Brennan and Pettit, 2005). While rejecting such an image of purely self-interested people as economists portray, devising institutional arrangements that are not sufficiently economically incentive-compatible is problematic for workable and stable institutions of (genomic) justice (Brennan and Pettit, 2005). People are not knavish and a principle that requires incentives as though we were would be too extreme. Nevertheless, we are not always motivated to an ideal level in order to comply with, or excel upon, socially just institutions (at least not all the time) nor, in so far as we do, could we simply be assumed to continuously do so over time and in all circumstances within which we find ourselves in the normal course of our lives. So far, nothing here seems particularly controversial. It only seems to suggest that the motivations of CRISPR patent-holders (who engage in ethical licensing) may not realistically be assumed to be purely other-motivated, or altruistic, but that they are also in it for commercial profitability, as well as other forms of incentives (such as winning a Nobel Prize).

However, insofar as such feasibility constraints are taken as limitations on what is realistic in terms of social justice, these limitations themselves must be subjected to critical scrutiny. What is feasible depends greatly on the balance between self-interested and other-interested motivations and, consequently, such feasibility constraints not only form the parameters of what can be done, they are also the consequences of what is done. The concern, akin to that of Titmuss (1971) regarding blood donation, is

⁵Although John Rawls famously stands accused of being too ideal, he does note that any proposal or theory regarding justice must take due account of the “strains of commitment” where people should only be expected to act according to reasonable social rules, including accommodating a reasonable level of self-interest.

that this use of incentives would lead to a “crowding out” of social (or other-regarding) preferences, which, while arguably productive in pursuing social justice goals in the short term, would undermine such goals in the longer term.⁶ As noted above, the ongoing process of academic norm contestation and movement toward commercial interests, that Lee suggests (2013), may also be a symptom of such “crowding out” dynamics. It may be the case that sometimes the gain from more economic incentives more than compensates for the loss in social preferences. In any case, it seems that the momentum in the context of new gene-editing technologies, such as CRISPR-Cas9, is increasingly toward the ethos of the private sphere, and away from the ethos of (purer) scientific collaboration (Sherkow, 2016). The concern is that this may increasingly “crowd-out” social (other-regarding) preferences and undermine the motivational structure conducive to the potential of “ethical licensing” as a sustainable alternative to the traditional forms of regulation.

Overall, while we note some immediately apparent advantages to the ethical licensing approach (i.e. epistemic, speed, flexibility, global reach, and court enforced), it is not clear that these outweigh the potential problems in terms of lack of democratic legitimacy and procedural justice, problems in maintaining voluntariness, wider/global coordination, and sustainability/stability, particularly with the potential for adverse motivational effects/problems over time. If they do, some response will be needed to address these challenges.

Patents in the Public Sphere?

Some of these concerns seem potentially to be addressed by another emerging patent-based approach. Parthasarathy (2018) proposes government-driven regulation using the patent system, which, she argues, has more transparency and legitimacy than the ethical licensing approach. Rather than ethical licensing by private actors, Parthasarathy is seeking a more formal, comprehensive and government-administered regulation using the patent system. Citing the EU’s 1998 Directive on the legal protection of biotechnological inventions, as well as other historical examples of government run patent control, a key model was highlighted by the US Congress’ use of the patent system to control the development and commercialisation of atomic weapons in the 1940s. Some relevant technologies would be patentable, some subject to compulsory licences if in the public interest and some excluded from patenting entirely (e.g. atomic weapons). This would be managed by an advisory committee for gene-editing patents—including (in the US case at hand) members of EPA, health sector, commercial sector and others, in conjunction with members from the US Patent Office. This advisory committee would guide this government-driven approach in terms of deciding when to

exert control over gene editing patents. There seem to be some apparent advantages with this approach (over traditional regulation and over the ethical licensing approach above—speed and stability being central, as well as increased democratic legitimacy, at least *via* this committee). However, problems also arise—such as a “half-way house” of global democratic legitimacy that may not be legitimate enough whilst still compromising the speed of decision-making under the ethical licensing approach. The problem here is that this addition to traditional regulation does not seem to improve things from mere reliance on that same traditional regulation itself. The problem of achieving agreement in terms of the ethical, legal and societal implications of such technologies or applications of technologies; in terms of devising the appropriate level of fostering or restriction of such technologies, or parts of such technologies, will be present in this approach, albeit focussed on the aforementioned advisory committee. If the decision-making process is still easier in the committee, the membership of this committee will become the new area of contention. If this is all avoided, by the top-down arrangement of such a committee (whether by government or state body) then there is an issue of a lack of democratic accountability, oversight, and engagement. Whether or not genome editing of humans is to be welcomed, the assessment will entail the same challenges as existing democratically legitimated approaches to creating regulation. If this is short-circuited in some way, then that very democratic legitimacy may be damaged. Given the profound societal impact that can be anticipated, and the strong emotions and reactions that it can provoke, the wider acceptance of this technology could be damaged by the sense that it “slips in by the back door”. This route also loses the dynamic aspects of the ‘private ethical licensing’ route—it may require wider levels of compromise, or consensus, that one or a few patent owners can swiftly sidestep, albeit with even greater loss to democratic legitimacy and oversight, as well as the concerns over motivations outlined above.

An International Patent-Based Approach: TRIPS and the WTO

Even with its various problems—speed being the key one - the legislative and regulatory route remains an important, if not the most important, approach in responsible governance of new technologies. One important concern is whether a focus on some patent-based alternative lessens the urgency for, or interferes with, the more robust, regulatory/legislative approach. Adopting either the private governance model or Parthasarathy’s alternative does not seem to be an adequate alternative in this regard. This does not rule out various mixed approaches which may strike viable balances (Guerrini et al., 2017; Sherkow, 2017). In fairness, Parthasarathy (2018) does not see her suggestion as a comprehensive alternative to traditional regulation but argues that it should be part of a comprehensive approach. Whatever the combination involved in such a mixed approach, there is no reason to be confined to using the current patent environment as the default framework. In Feeney et al. (2018), we advanced a number of proposals for relatively realistic, yet substantial, reform of the patent-based environment limiting the ability of the patentee to exclude others from performing work with the patent invention, including restrictions on the technological field in which rights may be exercised and on the types of activity which

⁶Benabou and Tirole (2006) note evidence that suggests that the provision of economic rewards and punishments to people in order to foster prosocial behaviour sometimes has a perverse effect of reducing the total contribution those people have been previously providing. They note that a crowding out of “intrinsic motivation” by extrinsic incentives has been observed in a variety of cases. Indeed, provisional evidence even suggests that explicit incentives diminish activity in distinct regions of the brain associated with social preferences (Bowles and Polania Reyes, 2009). See also Michael Sandel’s chapter on “How markets crowd out morals” in Sandel (2012): 93–130.

can be constrained and, importantly, a restriction on the period for which the patentee can impose exclusivity in the first place (44–46). Whatever the various suggestions for realistic reforms of the existing patent landscape may be, the key point is that such reforms may be needed if there is to be a sustainable inclusion of patent-based approaches that will contribute to the traditional regulatory options whilst as the same time, not interfering with this same objective, for instance, by increasing the power of biotechnological companies.

With gene editing, we see two dominant concerns—safety and justice in access. As regards safety, this has two aspects: safety of society as a whole; and, for human editing, safety of the edited individual and her offspring. Safety, with gene editing, has an international dimension since the edited species are at least potentially mobile—they can cross borders, bringing risk to countries beyond those where the gene editing occurs unless export is only of dead or sterile organisms. For fish, birds, pollen, seeds, and many small animals, it may be impossible to prevent border crossing, and for humans the lessons of medical tourism show us that preventing border crossing by edited humans may likewise be impossible. Thus, while, from an international point of view, it may be acceptable to allow countries to make their own decisions regarding gene editing of species which can be prevented from crossing borders alive, for many species we do not have this luxury. Thus, enforceable international regulation seems to be essential, and patent-related governance should be seen only as a, albeit necessary, stop-gap measure.

Ethical licensing, unless mandated by law, can only be an inadequate partial solution as a result of its voluntary nature. Ad hoc national restrictions on patentability, even though these might include constraints on local and international licensing, suffer from the slowness of bureaucracy and the voluntariness of ethical licensing (e.g. a company may choose not to patent in countries with such ad hoc constraints). Nonetheless, even ad hoc patentability constraints would add to the currently inadequate patchwork of international governance.

Revision of TRIPS and of the mandate of the WTO, however, does offer the opportunity to introduce constraints on patentees on a near-global scale without the delays fundamental to international regulation of the performance of gene editing, constraints that could at the same time address the question of justice of access. Thus, a revised TRIPS might allow signatory members to adopt measures proposed ad hoc by a majority of a WTO ethics advisory committee while still allowing other signatory members to avoid imposing such constraints on their national patents. With enough signatory members adopting constraints extending to the activities of patentees and their licensees in other countries, patentees might well be forced to accept constraints globally.⁷

Thus, should such a WTO ethics committee recommend X then any country might require that patents should not be granted in

their country unless the patentee agrees to X globally and requires its licensees to do the same. X might include not using the technology in a particular way or the granting of non-exclusive licences to the technology available to all in that country, group of countries, or anywhere. Local enforceability of any patent might also be linked to compliance with any future WTO ethics committee recommendation adopted by the country in question. A patentee would then be required to choose between continuing with its existing practices or maintaining local patent enforceability. The patentee could then wait until the need to enforce its patent locally arose before changing its practices.

To deal with “rogue” actors in “rogue” countries, the WTO recommendation might include requiring patentees to grant third parties royalty-free licences not to operate under a patent in a “rogue” country but to sue the “rogue” actors in that country. Thus if Broad were to have a patent in Ukraine, such a licensee might be appointed to sue the “rogue” clinic at its own cost. Of course, any proposal or regulatory approach—patent-based or otherwise—will unlikely eliminate all forms of rogue actors or rogue actions. However, the addition of our proposal to the range of regulatory instruments available should further decrease the room for such actors to successfully operate.⁸

CONCLUSION

In this paper, we argue that gene editing requires regulation and that this ideally would involve enforceable international legislation. However, we accept that the road to such legislation is long and that even after acceptance it would lack adequate flexibility. We consider the ethical licensing approach to be commendable and that it should be encouraged; however, it is insufficient. Parthasarathy’s ad hoc national modification of patent laws is likewise commendable but insufficient. We argue instead for an amendment of TRIPS and the equipping of the WTO with an

⁸It is worth noting how our proposal should respond to some concerns recently raised by Justine Pila in two papers offering alternative proposals for the regulation of the patenting and licensing of emerging technologies (Pila 2020a; Pila 2020b). In the first paper, Pila argues that the approach of the European Patent Office (EPO) to the interpretation of the morality clause [Article 53(a)] of the European Patent Convention) is “incoherent, unduly restrictive and blind to the regulatory challenges presented by emerging technologies” and that the risk assessment of that clause “necessitates an epistemic and deliberative process aimed at recognizing and confronting the uncertain consequences of new technologies and their implications for society.” (Pila, 2020a), 535-6. To do this, she argues, the EPO and the domestic patent offices should introduce a version of the risk assessment model proposed in a brief prepared by the University of the West of England in 2017 for the European Commission and create a “morality and public policy triage system” within those patent offices, i.e. implicitly a system operated by the patent offices themselves. In the later paper, Pila goes on to propose the extension of the “fair, reasonable, and non-discriminatory” (FRAND) licensing system currently operated on a voluntary basis by industry-based standard-setting organizations. Recognising the danger of a voluntary system operated by industry itself, Pila acknowledges that such an extension of the FRAND system should be compulsory for some technologies and that some other means would have to be found for identifying the patents to which such a FRAND-like system would be applied. For medicines, she implicitly identifies the WHO as a possible candidate. (Pila, 2020b), 15-8.

⁷Each technology that would be put to such a committee would inevitably raise major lobbying/self-interest concerns in some countries and therefore we suspect that such a committee would have to have delegates from each country or group of countries, eg. grouped according to their level of economic development, geographic location, or population size. Inevitably, these will be political appointees, perhaps supported by a secretariat provided by WTO. Of course, there will be difficulties and challenges here—and with any proposal that seeks to revise TRIPS—we do not attempt to address such issues here.

ethics advisory committee whose majority recommendations can be adopted (or not) by individual WTO signatory countries.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

OF conceived of the paper and wrote the first draft of the manuscript. JC and SS added crucial sections to the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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FUNDING

We acknowledge support by Open Access Publishing Fund of University of Tübingen. OF work is supported by the Hans Gottschalk-Stiftung.

ACKNOWLEDGMENTS

Many thanks to Gardar Árnason for reviewing the final draft and also to the two reviewers for their helpful comments. OF presented an earlier version of this paper at the International Conference Transformative Technologies: Legal and Ethical Challenges of the 21st Century, Banja Luka, Bosnia and Herzegovina. (February 7–8, 2020) and wishes to thank both organisers (especially Igor Milinković) and participants who positively contributed to the current work.

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