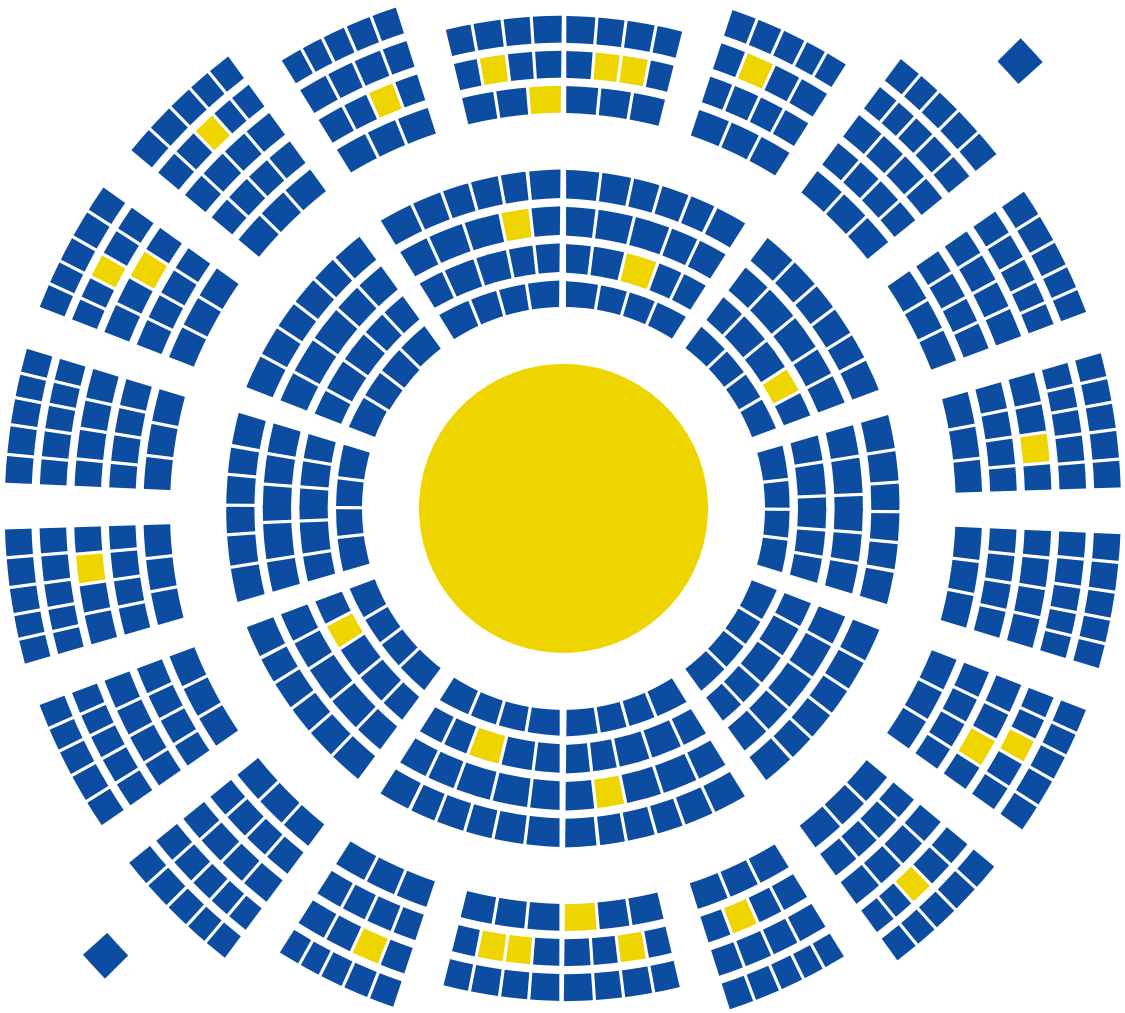
REGULATION AND GOVERNANCE OF GENE EDITING TECHNOLOGIES (CRISPR, ETC.)

EDITED BY: Alberto Asquer and Michael Morrison
PUBLISHED IN: Frontiers in Political Science



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ISSN 1664-8714
ISBN 978-2-83250-391-1
DOI 10.3389/978-2-83250-391-1

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REGULATION AND GOVERNANCE OF GENE EDITING TECHNOLOGIES (CRISPR, ETC.)

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Citation: Asquer, A., Morrison, M., eds. (2022). Regulation and Governance of Gene Editing Technologies (CRISPR, etc.). Lausanne: Frontiers Media SA.
doi: 10.3389/978-2-83250-391-1

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frontiers | Frontiers in Political Science

TYPE Editorial
PUBLISHED 20 September 2022
DOI 10.3389/fpos.2022.1027410

OPEN ACCESS

EDITED AND REVIEWED BY
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SPECIALTY SECTION
This article was submitted to Politics of Technology, a section of the journal Frontiers in Political Science

RECEIVED 25 August 2022
ACCEPTED 02 September 2022
PUBLISHED 20 September 2022

CITATION
Asquer A and Morrison M (2022) Editorial: Regulation and governance of gene editing technologies (CRISPR, etc.). *Front. Polit. Sci.* 4:1027410. doi: 10.3389/fpos.2022.1027410

Editorial: Regulation and governance of gene editing technologies (CRISPR, etc.)

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KEYWORDS

gene editing, CRISPR, regulation, governance, public participation

Editorial on the Research Topic
Regulation and governance of gene editing technologies (CRISPR, etc.)

"Gene editing" describes a range of tools and techniques in molecular biology that permit scientists to make directed changes to the genetic material of any living organism. Gene editing can be understood as a "gateway technology;" these techniques offer versatile, accessible tools for use in experimental settings, and they have a wide range of potential applications in diverse sectors. Techniques for modifying DNA have been in use since the 1970s, while early gene editing techniques first emerged around 30 years ago. However, it was the identification in 2012 of CRISPR/cas9 gene editing by a research group led by Jennifer Doudna and Emmanuelle Charpentier (Jinek et al., 2012) that catalyzed the current global explosion of interest and activity in gene editing. CRISPR, which stands for Clustered Randomly Interspersed Short Palindromic Repeats, acts faster and is cheaper and easier to make and use than other genetic modification or gene editing tools. The skills and equipment needed to use CRISPR can be found in most academic and commercial life sciences laboratories, and CRISPR components were rapidly made available at low cost through existing channels for distributing biological reagents (Martin et al., 2020). The preceding 40-plus years of research and commercial activity with genetic engineering technologies also served to identify a considerable range of applications or suggest new avenues for development where CRISPR might improve on existing genetic modification practices. Accordingly, global research on gene editing, as indicated by the number of publications (Asquer and Krachkovskaya, 2021; Zhou et al., 2021) and patent filings (Bicudo et al., 2022), has demonstrated a steep increase since 2012. From being a niche research interest, gene editing must now be considered a field of international scientific, commercial, and increasingly, public interest (Martin et al., 2020).

As is now commonplace with emerging technology fields (and here we might think of artificial intelligence or nanotechnology), CRISPR/cas9 gene editing was heralded with considerable promise in both the popular and scientific press (Ledford, 2015; Maben, 2016). Gene editing can be applied in almost all organisms, from plants and

microorganisms to humans and other animals. The areas of potential application range from human health and reproduction to agriculture, industrial manufacture (for example of biofuels), control of harmful or invasive species, and other, emerging possibilities such as biocomputing (encoding data in living systems), recreating extinct species, biowarfare and bioterrorism, and do-it-yourself biology also known as bio-backing where individuals conduct experiments outside formal institutional settings (Dimond et al., 2021). However, many actual or prospective applications of gene editing have also provoked considerable concern and unease.

Most notably, and egregiously, in November 2018, He Jiankui, a scientist based in China, reported to a global audience the birth of the world's first genetically edited babies. Reproductive, or "germ line," genetic modification has been viewed as ethically unacceptable since the early days of genetic modification and is prohibited by law in many jurisdictions (Isasi et al., 2016). Unsurprisingly then, Jiankui's actions led to a considerable amount of international condemnation and commentary, and also, eventually to a custodial sentence for Jiankui himself (Rosemann et al., 2019). Nonetheless, the possibility of heritable genetic modification of humans is now a reality rather than merely a possibility and must be contended with (Martin and Turkmendag, 2021).

In the field of agricultural biotechnology, the advent of CRISPR/cas9 gene editing also gave new animus to another controversial issue from a prior era of genetic technology, genetically modified organisms (GMOs). The most pressing question for many scientists and companies was whether a new generation of gene edited crops would fall under existing legislation for the production and release of GMOs. Different jurisdictions have adopted divergent approaches: the US Department of Agriculture (USDA) opted not to subject gene editing crops to additional regulation provided the gene editing technique does not introduce "novel" DNA into the modified organism, while the EU has ruled that all gene edited plants and animals fall under its existing GMO directives (Callaway, 2018; Wolt and Wolf, 2018). The latter decision has proved particularly controversial and has provoked a range of proposals (and demands) to reform EU legislation (Ricroch and Hénard-Damave, 2016; Garland, 2021).

Another potential non-human application of gene editing is to create so-called "gene drives" that enable a genetic modification to be transmitted from one organism to another through normal sexual reproduction, potentially enabling large-scale modification of whole populations of organisms in the wild (Rabitz, 2021). The main anticipated aim is to control populations of pest organism such as invasive non-native species or "crash" populations of malaria-transmitting mosquitos. However, gene drive organisms need to be released into the wild, outside a controlled environment, which poses considerable challenges for governance, not least as modified organisms cannot be expected to stay within national jurisdictions (Oye et al., 2014; Rabitz, 2021).

Whilst not an application *per se*, the patent rights to CRISPR/cas9 have also been subject to a protracted dispute (Sherkow, 2017; Panagopoulos and Sideri, 2021), while the patenting strategy of the CRISPR patent holders has also been subject to ethical critique for its potential impacts on innovation (Feeney et al., 2018; Panagopoulos and Sideri, 2021; Bicudo et al., 2022).

This is an illustrative, rather than an exhaustive list, but it is sufficient to evoke the range of governance and regulatory challenges raised by the advent of gene editing technology, which also form the basis for this thematic collection. The title of this collection "*Regulation and Governance of Gene Editing Technologies (CRISPR, etc.)*," should not be taken to imply that it is necessarily gene editing technology *per se* that requires regulatory scrutiny (Moses, 2016). It is better read as a shorthand for a more nuanced debate, about the role of regulation in steering the (sociotechnical) systems and environments in which gene editing technology is developed into (largely commercial) products and services. Gene editing research and development is taking place in many countries, with human health and agriculture being the main commercial sectors so far. Accordingly, the papers in this collection come from authors from various nations, including the US, France, Germany, Japan, Australia, and Belgium, and the collection includes articles on governance and regulation of both human and animal gene editing.

The papers of this Research Topic can be positioned around four main themes, namely the analysis of genome editing debate, the design and assessment of regulatory tools, the role of Responsible Research and Innovation, and the integration of the regulatory and governance system for genome editing.

Two papers of this Research Topic analyse the features of the contemporary debate on gene editing. The contribution of Meyer and Vergnaud shows that governance and regulation of gene editing has been discussed across an increased number of disciplines and countries over the years. The debate gradually shifted away from reflections on the potential applications and benefits of gene editing toward calls for policy actions and regulatory interventions. The authors also notice that the public is portrayed in different ways ranging from recalcitrant subjects that must come to accept the use of gene editing to parts of the civil society that should be involved and engaged in a democratic debate on the use of gene editing. The issue of public engagement is specifically tackled by Iltis et al., who investigate the ethical roots of sources of substantive disagreement about appropriate research pathways and permissible clinical applications. They also identify five ideals that should guide the engagement of the public and stakeholders in science policy development, namely that engagement efforts should be comprehensive, transparent, inclusive, methodologically sound and accountable.

Three other papers of this Research Topic contribute advance scholarship on the design and assessment of regulatory tools in the field of gene editing, specifically dealing with patenting and marketing authorization. The study of Scheinerman and Sherkow provides a review and assessment of the various governance choices over patenting in gene editing. The authors observe that patents covering many of the most controversial applications of gene editing are regulated *via* non-democratic or anti-democratic institutions, such as private restrictions on licensing, while other patents that are more broadly related to democratic deliberation, like compulsory licenses, are poorly aimed for particular applications. The lack of democratic legitimacy is also discussed in the contribution by Feeney et al., who critically assess the advantages and disadvantages of three forms of governance of gene editing—namely, traditional regulation, ethical licensing and Parthasarathy's (2018) patenting system—before offering some amendments of Trade-Related Aspects of Intellectual Property Rights (TRIPS) and an alternative proposal of a WTO ethics advisory committee. The contribution of Nielsen et al., instead, provides an assessment of market authorization for gene edited products with respect to canons of public participation, transparency and accountability. Building on the analysis of the regulatory pathways of the US Food and Drugs Administration, the European Medicines Authority, and the Australian Therapeutic Goods Administration, the authors propose to incorporate principles of citizens participation into the regulatory process for the review of products of gene editing.

Two additional papers of this Research Topic focus on the role of Responsible Research and Innovation (RRI) in gene editing in different country contexts. The study by Kuzma and Cummings investigates attitudes toward RRI in the US in order to explore the possibility to establish coalitions on the conduct of gene editing research and applications. The authors highlight that positive attitudes toward principles and practices of RRI are associated with egalitarian cultural beliefs and higher levels of experience, and are negatively related to professional affiliation with industry or trade organizations. The work of Müller et al., instead, examines attitudes toward RRI in Germany. The authors show that agricultural stakeholders in a project that was intended to promote RRI in Bavaria expressed their skepticism toward the adoption of gene editing in Bavarian livestock agriculture. They conclude by discussing the importance of redistributing benefits among stakeholders to ease tensions between policy fields or circumvent other contextual constraints.

Finally, two papers of this Research Topic address the issue of the fragmentation of regulation and governance gene editing. The contribution by Mahalatchimy and Rial-Sebbag analyses the divisions, splits, and segmentation of the regulatory landscape for human germline editing in the EU (and France in particular), which they relate to historical and technicolegal reasons. The study of Minari et al., instead, looks at the reasons for the fragmentation of the regulatory field of gene editing in Japan and at the constraints to harmonization that arise from the tension between national and international approaches. The authors conclude by proposing a contiguous governance model that attends to both geopolitical (i.e., synchronic) and historical (i.e., diachronic) perspectives.

Taken together, the articles of this Research Topic address central concerns in the regulation and governance of gene editing, namely ensuring the participation of the public and stakeholders in identifying issues posed by gene editing technologies and approaches that should be adopted in related research and applications. Further research along these lines will help foster a democratic debate on the use of gene editing, cultivating trust toward scientists and public officers, and promoting the welfare of society at large over the exclusive pursuit of private interests.

Author contributions

Both authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

Funding

The contribution of MM was supported the Leverhulme Trust under Grant No. RPG-2017-330 BioGOV; Governing biomodification in the life sciences.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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frontiers in Political Science

ORIGINAL RESEARCH
published: 24 June 2021
doi: 10.3389/fpos.2021.677003

Cultural Beliefs and Stakeholder Affiliation Influence Attitudes Towards Responsible Research and Innovation Among United States Stakeholders Involved in Biotechnology and Gene Editing

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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: *07 March 2021*
Accepted: *14 June 2021*
Published: *24 June 2021*

Citation:
Kuzma J and Cummings CL (2021) Cultural Beliefs and Stakeholder Affiliation Influence Attitudes Towards Responsible Research and Innovation Among United States Stakeholders Involved in Biotechnology and Gene Editing. Front. Polit. Sci. 3:677003. doi: 10.3389/fpos.2021.677003

Biotech developers are concerned about the future of gene editing having experienced the contentious history of first-generation GM foods. They have also expressed desires to do better with public engagement in gene-editing innovation. The framework of Responsible Research and Innovation (RRI) may provide a way forward to act on their desires for greater public legitimacy. However, in the United States, -there has also been reluctance to incorporate RRI into biotechnology innovation systems like gene editing in food and agriculture. In this article, we investigate individual- and group-level factors, including demographic, sociographic, and cultural factors, that influence attitudes towards RRI among biotechnology United States stakeholders. Using the Advocacy Coalition Framework's (ACF) hierarchy of beliefs as a theoretical guide, biotechnology stakeholders (n = 110) were surveyed about their cultural (deep-core) beliefs and then about their attitudes towards principles (policy-core beliefs) and practices (secondary beliefs) of RRI applied to biotechnology innovation. Through statistical analysis of the results, we found significant relationships between stronger egalitarian cultural-beliefs and positive attitudes towards both the principles and practices of RRI. We also found that participants with higher levels of experience held more positive attitudes towards principles of RRI. In contrast, we found a significant inverse relationship between professional affiliation with industry or trade organizations and attitudes towards RRI practices. With these results, we present a model of factors that influence RRI attitudes for future testing. In closing, we interpret the results in the context of ACF to examine the potential for building cross-sector coalitions for practicing RRI within United States gene-editing innovation systems.

Keywords: responsible research and innovation, gene editing, genome editing, oversight, regulation, stakeholders, attitudes, advocacy coalition theory

INTRODUCTION

Scholars proposed the framework of responsible research and innovation (RRI) in the last decade to expand the governance of emerging technologies beyond traditional questions about the downstream risks of technological products to upstream questions about research and innovation processes themselves (Stilgoe et al., 2013). In particular, Stilgoe et al. (2013) notes that public controversies about science and technology "cannot be reduced to questions of risk, but rather encompass a range of concerns relating to the purposes and motivations of research" (p. 1569). RRI seeks to better align scientific and technological research and development with democratic processes, societal values and needs, and humility towards the future (e.g., Owen et al., 2012; Owen et al., 2013; Stilgoe et al., 2013). RRI arose out of a longer history of work on the ethical, legal, and social implications/aspects (ELSI in the United States or ELSA in the EU) of science and technology development (Felt 2018). RRI has been integrated into EU funding programs (Felt 2018) and has been the subject of much science and technology studies (STS) scholarship. However, it has not been significantly mainstreamed into S&T funding, research policy, or innovation systems in the United States.

Around the time that RRI emerged, the biotechnology sector underwent a revolution with the advent of gene-editing methods. Biotech developers are now concerned about the future of gene-editing having experienced the contentious history of first-generation GM foods (Marris et al., 2015; Kuzma 2016; Hartley et al., 2017; Kuzma 2018). For example, consumers are purchasing more non-GM and organic products, and food companies are seeking out non-GM ingredients (Malcolm 2016; Hartman Group, 2018). At the same time, biotech developers see gene-editing, such as through the use of CRISPR, as a way to alter crops for useful purposes while potentially avoiding public backlash and cumbersome regulation (Kuzma 2016; Kuzma et al., 2016; Kuzma 2018). Biotech developers indicate that they want to do a better job of bringing the public along with gene-editing innovation in comparison to how they proceeded with first-generation transgenic and GM crops (Kokotovich and Kuzma 2014; Kuzma et al., 2016; Kuzma 2018). They see gene-editing as potentially more acceptable to consumers, as gene-edited crops do not always include the introduction of foreign DNA into the final product. Some perception studies of GM crops and foods have shown that consumers indeed have fewer adverse attitudes towards the introduction of DNA from the same species (as can be achieved through gene editing) in comparison with the introduction of DNA from distantly related species (Mielby et al., 2013; Shew et al., 2018). A recent cross-national study of United States consumers concluded that people were more willing to consume CRISPR-based foods than 1st generation GM or transgenic foods, although both were viewed less positively than conventional foods (Shew et al., 2018).

Developers see gene-edited crops as a chance to start fresh with greater inclusion of public dialogue and education to address consumer acceptance issues. For example, in one study interviewing biotech stakeholders and developers, a majority expressed the need for the public to be engaged in gene-editing governance (Kuzma et al., 2016). In addition, a coalition of industry, non-profits, and trade organizations is emerging for verification of responsible practices for gene-editing in agriculture (Center for Food Integrity, 2020). At the same time, United States regulatory systems for gene-editing, like gene-edited foods, are evolving in different directions. For example, in 2020, the United States Department of Agriculture passed new regulations for GM crops which exempt many gene-edited crops from pre-market oversight (USDA 2020) and lack requirements for public disclosure when they enter agricultural or food systems (Jaffe 2019; Kuzma and Grieger 2020).

In the absence of federal mandates for public transparency and disclosure of gene-edited products, RRI principles and practices may provide a way forward for biotech developers to act on their desires for greater public engagement and legitimacy. The most cited article on RRI (according to Google Scholar) frames it according to four principles: anticipation, inclusion, reflexivity, and responsiveness (Stilgoe et al., 2013). *Reflexivity* moves governance of science and technology away from solely a risk-based approach to one that encompasses reflection on the underlying goals, motivations, limits of knowledge, assumptions, and alternative framings of problems. *Anticipation* incorporates considerations where potential future consequences can be analyzed and explored prior to technological development, allowing for improved consideration of downstream risks and impacts. *Inclusion* prioritizes opening up governance of research and innovation to incorporate the perspectives of diverse publics, which provides more varied, reflexive, and anticipatory approach than the traditional inclusion of subject-matter experts alone in governance systems. Finally, *responsiveness* demands the ability to alter the direction or scope of innovation given changing circumstances, new data, or emergent stakeholder and public values. The RRI framework based on these four principles is "deemed to be characteristic of a more responsible vision of innovation" than other frameworks centering on research ethics, diversity and inclusion in STEM fields, and interdisciplinarity and has been "operationalized by national funding bodies" and "integrated in research practice" in the EU (Wittrock et al., 2021, p. xi).

In previous work (Roberts et al., 2020), we developed quantitative survey questions to measure attitudes towards the four RRI principles from Stilgoe et al. (2013) and towards ways to put these principles into action. We found that United States stakeholders promoting or developing biotechnology innovations--industry, trade organizations, and academics--had more negative reactions to RRI principles of inclusion and responsiveness than the RRI principles of reflexivity and anticipation in comparison to government and advocacy groups (i.e., consumer or environmental non-profits). These results were further explained by qualitative focus group research with these stakeholders. We found that biotech developers and their proponents (i.e., biotech or commodity-crop trade organizations) were wary of giving voice or choice to groups outside innovation pipelines, which contradicts RRI principles of inclusion and responsiveness (Stilgoe et al., 2013). Biotech developers expressed fears that these facets of RRI would

slow their work down in the face of pressures to move quickly to compete for funding, capital, and national or international professional advantages (Roberts et al., 2020).

While this previous study observed differences in RRI attitudes among stakeholder groups and provided some insights into why stakeholder groups feel differently about RRI, it did not adequately describe what individual-level or group-level factors influence differences in attitudes for RRI among stakeholders. Thus, in this paper, we examine whether demographic, cultural, professional, or other sociographic factors affect individual and group attitudes towards RRI principles and practices. Our work is also guided by the Advocacy Coalition Framework (ACF). ACF is a theoretical framework from the policy process literature that examines how individual- and group-beliefs relate to the formation and operation of coalitions within policy arenas (Jenkins-Smith et al., 2014) (see more discussion on ACF and our survey questions below in Methods). In this study, we use the ACF structure for core, policy, secondary "beliefs" and the principles of RRI from Stilgoe et al. (2013) to develop survey questions in order to gain insights into factors that influence attitudes towards RRI among United States stakeholders in biotechnology innovation. We then use the ACF to hypothesize about the potential to form wider coalitions across United States stakeholder groups to incorporate RRI into United States gene-editing innovation systems.

To set the stage for this work, we first review key previous studies on RRI in biotechnology or related innovation systems and then turn to a deeper discussion of the ACF and how it relates to beliefs about RRI and United States stakeholder coalitions in biotechnology innovation systems.

Previous Work on Biotechnology and RRI

A few previous studies have specifically considered stakeholder attitudes towards RRI within United States biotechnology innovation systems. Two studies used interviews with academic researchers. Doezema and Guston (2018) interviewed United States biotech innovators within a single university research institute. In this study, RRI was framed according to areas of practice that could be put into place at the institute—that is, ethics, science education, open science, societal engagement, gender equality, and diversity. The study found that although ethics was of interest to biotech researchers at this institute, RRI was conceived as traditional "research ethics" such as reproducibility and misconduct, rather than according the Stilgoe et al. (2013) RRI principles. A second study (Glerup et al., 2017) interviewed eleven United States academics working in synthetic biology and nanotechnology using a Socio-Technical Integration Research (STIR) protocol where STS researchers embed themselves in laboratories (Fisher and Schuurbiers 2013). They found that the researchers thought of "responsibility" in more traditional ways, such as producing good science and taking care of employees, rather than broader obligations and responsivity to society (Glerup et al., 2017). Neither of these studies employed survey methods or empirically compared United States biotechnology stakeholder-group attitudes as we do in this article.

Other reports focus on attitudes of innovators in the EU, Canada, and United Kingdom towards RRI. Marris et al., 2015 identified engineers and natural scientists' conceptions of RRI within the synthetic biology community in the United Kingdom. They found that seeking greater public acceptance of synthetic biology was the primary motivation for RRI. Similarly, Hartley et al. (2017) interviewed university researchers across STEM fields working in the United Kingdom and found that various actors espouse different meanings of RRI, although a predominant theme was the protection of scientific research from politics. For example, several researchers felt that public inclusion and engagement would best serve to increase public understanding of science and thus garner support for GM work (Hartley et al., 2017); rather than serve to give publics a "voice" in the conduct of GM work, like "inclusion" is meant to do in Stilgoe et al. (2013).

Along similar lines, Carrier and Gartzlaff, 2020 interviewed 80 researchers and research executives across the EU in a variety of technological fields across social and natural sciences, humanities, and engineering to investigate their understandings of RRI. While they found a welcoming attitude towards RRI in general, the interviewees were concerned about granting societal actors influence on the direction of research and innovation given public "ignorance and bias," the additional expenditures that may be required to engage societal actors, and the potential loss of autonomy for science. Another study in Canada interviewed 31 people who design, develop and commercialize health innovations about practices of RRI (Rivard and Lehoux 2020). The study found that although innovators generally agreed on the desirability of several principles of RRI, they were concerned about the feasibility of meaningful implementation of them. The findings in these last two studies are consistent with our previous study with United States biotechnology stakeholders (Roberts et al., 2020), in which we found greater agreement on RRI principles (i.e., anticipation, responsivity, reflexivity, and inclusion) among diverse stakeholder groups than on specific RRI practices for implementing these principles.

RRI for biotechnology has also been investigated in multiple case studies using anthropological approaches to observation (see Macnaghten, 2016). For instance, Macnaghten, 2016 used ethnographic work to identify RRI attitudes towards GM food crops in Brazil, Mexico, and India as well as among symposium attendees in the United Kingdom and EU (Carro-Ripalda and Macnaghten 2015). These studies report the cultural, institutional, and social challenges to enacting RRI and provide greater identification of the practicality of enacting RRI within synthetic biology research and innovation (Macnaghten, 2016). In the context of GM crops, they found that in situations where the crop was not culturally significant to the country, like soybean in Brazil, scientists had "clear and unqualified optimism . . . on the role of GM crop technologies, with little evidence of a structured and sustained debate with wider society" (Carro-Ripalda and Macnaghten 2015; Macnaghten, 2016, p.284). In India, they heard from crop scientists who argued that India "could not afford the risk of falling behind in the development of biotechnology" and that anti-GM groups were "ignorant" (Carro-Ripalda and

Macnaghten 2015, p 25). These results are similar to the barriers identified in our previous work with focus groups of United States biotechnology stakeholders (Roberts et al., 2020). Here we found 1) "cynicism" among innovators with regard to the public's ability to engage in informed conversation and 2) the predominance of "academic capitalism" in United States culture and institutions, through which any process such as RRI that might slow innovation down would reduce competitiveness and be seen as undesirable.

All the studies mentioned above used qualitative methods of inquiry, and only a few focus on United States biotechnology innovation systems. In contrast, in this paper, we use quantitative surveys to investigate the relationships between demographic, sociographic, professional, or cultural factors and their influence on attitudes towards RRI. Furthermore, this paper breaks new ground by merging RRI scholarship and quantitative survey methods with policy process theory (namely the ACF), where we evaluate survey data with a larger sample (n = 110) of multi-sector stakeholders in United States biotechnology innovation. To our knowledge, our study is unique in these regards in the field of RRI scholarship.

Relating RRI Attitudes to the Advocacy Coalition Framework

A significant challenge faced by those attempting to legitimize and implement the RRI framework is establishing processes, strategies, and norms that create shared goals, while also facilitating coordination and cooperation between actors involved with innovation processes (Tait, 2017). ACF is a policy process theoretical framework that describes how actors engage in the policy process to translate their belief systems, which are simplified constructs used to make sense of the world, into public policy-making and action (Jenkins-Smith et al., 2014). This paper uses the theoretical lens of the ACF framework to explore whether United States stakeholders share beliefs related to RRI and thus whether those beliefs may translate into shared policy action to implement RRI in United States biotechnology innovation systems.

The ACF provides a framework for understanding how coalitions of actors within a policy subsystem (e.g., biotechnology innovation) may interact to affect change or maintain the status quo (reviewed in Weible et al., 2009). The ACF provides a three–tier structure for describing the beliefs of actors (e.g., in this study, our biotech stakeholders) within a policy subsystem (e.g., in this study, biotechnology innovation) (Weible et al., 2009) (**Figure 1**). *Deep core beliefs* are the broadest category of beliefs, represent the most stable beliefs of actors, and are mainly normative. They transcend policy subsystems, or in other words, actors hold these beliefs across multiple policy areas. For example, deep core beliefs represent liberal and conservative political beliefs, whether responsibility for progress lies with individuals or communities, and beliefs about future generations. The next level in the ACF hierarchy of beliefs are *policy core beliefs* which are more moderate in scope and relate to the substance of particular policy subsystems (in our case, biotechnology innovation). These beliefs are thought to be important for forming more stable coalitions in policy subsystems, and although somewhat resistant to change, they are more malleable than *deep core beliefs* in response to new information and experiences. Policy core beliefs include how problems are defined, the ordering of priorities, and balance between values such as economics and ethics. At the most specific level of ACF beliefs are *secondary beliefs* (**Figure 1**). These are narrower in scope than *policy core beliefs* and are often formed in response to empirical information or experiences within the policy subsystem. Secondary beliefs are those related to specific public policy instruments used to achieve policy outcomes. The ACF predicts that *secondary beliefs* are the most changeable among coalitions and actors within them (Sabatier et al., 2007).

The advocacy coalitions that exist within a subsystem are aggregated groups of actors that coordinate to a non-trivial degree in the pursuit of policy change (Sabatier et al., 2007). Under ACF, a shared set of motivations and beliefs are what bind coalitions together. Deep core beliefs, and to a lesser extent policy core beliefs, are seen under the ACF to hold advocacy coalitions together. Applying these ideas to the biotechnology policy subsystem, in this paper we wanted to see whether attitudes towards RRI principles, which relate to the ACF's level of policy core beliefs, and RRI practices, which relate to the ACF's level of secondary beliefs, were influenced by deep core beliefs and whether stakeholder groups differed in their deep core, policy core, and secondary beliefs (**Figure 1**).

Given the importance of deep core beliefs in understanding the behavior of advocacy coalitions within a policy subsystem, ACF scholars have devised a way to conceptualize and measure deep core beliefs that captures their normative and ontological nature, while also being testable and generalizable (Jenkins-Smith et al., 2014; Ripberger et al., 2014). These scholars used cultural theory (Douglas 1970; Douglas and Wildavsky 1982), to structure a scale for deep core beliefs that is generalizable across multiple policy subsystems. In this scale, twelve questions place survey respondents into four cultural archetypes--egalitarian, hierarchical, individualistic, or fatalistic (Ripberger et al., 2014). These cultural types, which are also considered "worldviews," have been previously defined by the intersection of the dimensions grid and group (Douglas 1970; Douglas and Wildavsky 1982). The grid dimension is a measure of beliefs about how society should be structured. It represents the degree to which individual behavior should be regulated by group pressure and structural constraints. The group dimension is a measure of feelings of group membership within society; for example, a high measure of group indicates that individuals have a strong feeling of association with others. In this study, we use the Ripberger et al. (2014) validated scale to probe whether our United States biotechnology stakeholders fall into the four cultural archetypes, as a measurement of deep core beliefs according to the ACF (see Methods and **Table 2**).

In our previous study (Roberts et al., 2020), we found significant differences among stakeholder groups especially in their attitudes to *secondary beliefs,* or in other words, ways of implementing RRI in biotechnology innovation. Industry and trade organizations rated inclusion and responsivity practices,

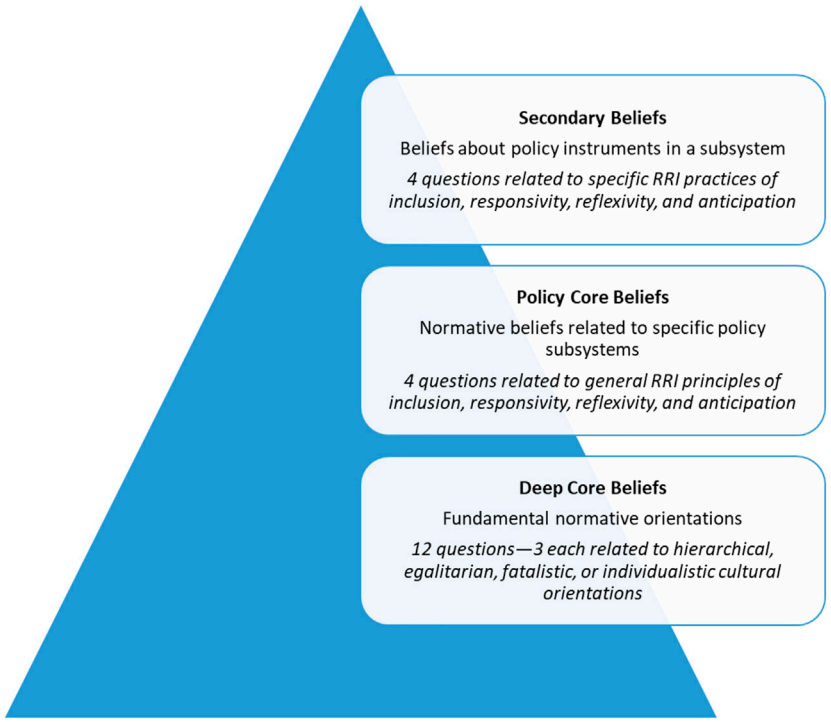

FIGURE 1 | ACF beliefs and relationship to stakeholder survey questions.

both which relinquish control to groups outside of biotechnology product development pipelines, less positively than government and advocacy groups. We found more agreement among stakeholder groups for the general principles of RRI, or *policy core beliefs,* applied to biotechnology innovation. As the ACF proposes that secondary beliefs are more flexible, and that shared policy core beliefs are important for stable coalition formation, we hypothesized that there are reasons to be optimistic about stakeholder groups in biotechnology innovation coming together to adopt RRI principles (which they share more agreement on) *if* better ways to implement them could be agreed upon (than those asked in the survey). However, in this prior study, we did not analyze whether *deep core beliefs* influence attitudes of biotechnology stakeholders towards RRI in the biotech innovation system. We also did not assess whether demographic (e.g., gender, race, age) or sociographic (e.g. income, education, experience in profession) factors influence RRI attitudes. We also did not address whether United States stakeholder groups share deep core beliefs and whether they are important for coming to agreement on RRI. Considering these gaps, this study addresses the following key research question:

> *What demographic, sociographic, professional, and cultural factors (deep core beliefs) best explain the variance of observed stakeholder's responsible innovation 1) policy core beliefs and 2) secondary beliefs?*

We further describe our methods for addressing this key question below, followed by our results. Finally, we discuss the meaning of our results for the possibility of implementing RRI in United States biotechnology innovation systems.

METHODS

Recruitment and Survey Participants

We used a purposive sampling approach to recruit a diverse group of study-participants comprised of a variety of biotechnology professionals from different sectors. Participants were recruited from a sample of United States stakeholders in the greater Raleigh-Durham-Chapel Hill area (Research Triangle, NC). Recruitment was prioritized among professionals working in areas related to biotechnology in agriculture, food, or the environment. Many of the biotechnology developers recruited in the study work on emerging methods of genetic engineering, such as gene editing. The geographic region of the Research Triangle provides a host of diverse biotechnology and bioscience organizations. The Research Triangle is among the most active scientific and development regions in the United States and ranks second behind Boston Metropolitan region for life science expertise and development (Rose 2015). Participants reflect a fair representation of biotech stakeholders in this highly active biotech region. However, the participants do not comprise a statistical or geographic representation of the United States.

In our search we prioritized balanced representation from academe, advocacy groups (i.e., consumer and environmental groups), government, industry, and trade organizations

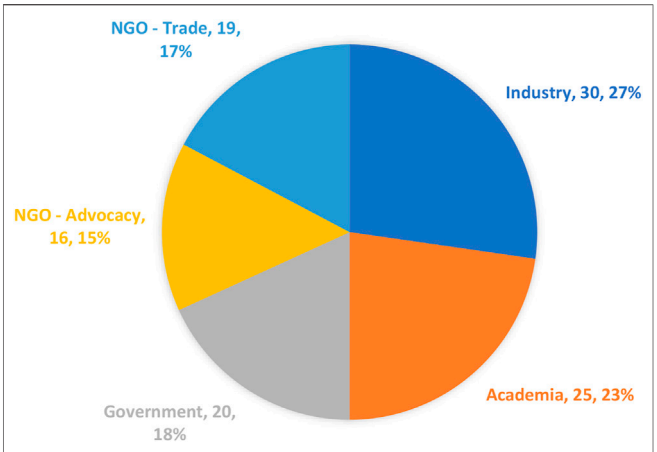

FIGURE 2 | Participants in biotechnology innovation by sector.

(i.e., industry and conventional farming non-profit associations), (**Figure 2**). We chose to split non-governmental organizations (NGOs) into advocacy groups and trade organizations to better reflect the abilities of each group--where advocacy groups may influence policy change and biotechnology oversight through media communications and legal precedence while trade organizations often seek change through more direct lobbying efforts on behalf of their constituencies (Kuzma 2013). Government representatives were engaged in biotechnology arenas related to policy-making, regulatory analysis, and risk assessment, within the topics of agriculture, food, health and the environment.

Participants were first identified from databases and listserves collated by the Genetic Engineering and Society (GES) Center at NC State and included professionals working in the Research Triangle Area. We used this group along with other collaborators and key contacts in a snowball sampling strategy to provide more names to expand our sampling frame. We also sought out website databases for non-governmental and governmental organizations in the region whose work relates to agricultural and environmental biotechnology as the existing database was lacking in these areas. The final sampling frame including over 700 professionals. Participants for this study were first emailed by a research team member to introduce the project and outline the opportunity for participation as well and review their rights as participants following university IRB guidelines (Exempt, NC State IRB Protocol Approval #6157). A second email was sent to those who did not respond and targeted phone calls were made to fill stakeholder groups that were underrepresented in previous invitation phases. The final sample included 109 completed responses. Each participant was offered a $50 dollar gift certificate for their time although some participants accepted less money or none at all in accordance with their agency rules. All processes of this study followed the IRB agreement as exempted by the host university.

Table 1 reports the demographic composition of the participant groups. Age ranged from 21 to 70 years old (M = 50.23, SD = 11.76) and professionals held a mean length of experience in their profession of 15.65 years (SD = 10.73). 34% were female, 14% considered themselves non-white, 60% held doctoral degrees, and median household income ranged between $101,000 - $125,000. **Figure 2** below also reports the sectors in which this group works. 100% of participants completed the agreed upon study and there was no apparent need for attention filter questions.

Data Collection

In order to assess our research question, data were collected using a pretested survey questionnaire (see Ripberger et al., 2014; Roberts et al., 2020). Survey questions were designed based on predominant elements of RRI (Stilgoe et al., 2013) and the application of cultural theory to test ACF deep core beliefs (Ripberger et al., 2014) as described above (**Table 2**). The survey was administered online using the Qualtrics platform. Participants were asked to complete the questionnaire which included the items reported on in this analysis (**Table 2**). The survey also elicited responses to open-ended qualitative questions relating to RRI, which we do not report in this paper. These qualitative results are being prepared for additional analyses.

Independent Variables

Independent variables tested are listed in **Table 1**. Demographic independent variables (IVs) include age, gender, and race (white/non-white). Sociographic IVs included on the survey and tested were education and income. Professional sector variables tested were sector affiliation (Trade, Government, Advocacy, Academe, and Industry) within the biotechnology innovation system and years of experience.

ACF deep core beliefs were measured based on cultural theory and the previously reported and tested scale (Ripberger et al., 2014) (**Table 2**; **Figure 1**). This independent variable represents the personal and cultural-value orientation held by individuals. We used deep core beliefs (aka cultural worldview) as an independent variable to see whether they predicted RRI attitudes—either towards general RRI principles (policy core beliefs) or suggested RRI practices (secondary beliefs) (**Table 2**). We also subsequently assess if deep core beliefs align with certain United States stakeholder groups. ACF posits that deep core beliefs are important for tight policy coalitions and are the least malleable. Given the contentiousness of the agricultural biotechnology domain and our previous findings of differences in stakeholder attitudes towards RRI (Roberts et al., 2020), we expected to observe differences in deep core beliefs among stakeholder groups and that they would strongly influence attitudes towards RRI.

Four distinct deep core value-orientations were measured based on Ripberger et al. (2014): *egalitarianism, fatalism, individualism* and *hierarchy* (**Figure 1**). Note that the questions that Ripberger et al. (2014) and we use do not directly measure group and grid dimensions from cultural theory (Douglas 1970; Douglas and Wildavsky 1982) but rather use twelve questions to place people into these four cultural types. We measured the four worldviews by asking respondents to identify their level of agreement with three 7-point Likert-scale items (1 = "strongly disagree," 7 = "strongly

TABLE 1 | Descriptive statistics for variables.

Descriptive Statistics of Independent and Dependent Variables	
Independent variables	
Age	M = 50.23; SD = 11.76
Gender	34% female; 66% male
Race	14% non-white; 86% white or caucasian
Education	Median "doctoral degree"
Annual income	Median "$101,000—$125,000 dollars per year"
Sector: Industry	27% (N = 30)
Sector: Academia	22% (N = 25)
Sector: Government	18% (N = 20)
Sector: NGO—advocacy	15% (N = 16)
Sector: NGO—trade association	17% (N = 19)
Years of experience within sector	M = 15.65 years; SD = 10.73
Core values: Egalitarianism	M = 4.26, SD = 1.36; Cronbach's α = 0.78
Core values: Fatalism	M = 3.15, SD = 1.22; Cronbach's α = 0.82
Core values: Hierarchy	M = 3.06, SD = 1.16; Cronbach's α = 0.73
Core values: Individualism	M = 3.43, SD = 1.12; Cronbach's α = 0.63
Dependent variables	
Responsible innovation policy core belief strength	M = 5.53; SD = 0.92; Cronbach's α = 0.69
Responsible innovation secondary beliefs	M = 4.89, SD = 1.26, Cronbach's α = 0.77

TABLE 2 | Survey questions to probe three tiers of ACF beliefs.

Deep core beliefs		**Policy core beliefs (principles)**	**Secondary beliefs (practices)**
12 questions (3 each)		***four questions (combined into one composite variable for RRI policy core beliefs)***	***four questions (combined into one composite variable for RRI secondary beliefs)***
1–7 Likert scale		***1–7 Likert scale***	***1–7 Likert scale***
Hierarchical	Inclusion	Maximizing public participation leads to better biotechnology policy.	Innovators should consult with consumers and advocacy groups during R and D in biotech.
Individualistic	Reflexivity	Reflecting on the underlying purposes, motivations, and uncertainties that surround biotechnology products is important.	Social scientists, environmental and health risk analysis and ethicists should be involved from the early stages of biotech innovation.
Fatalistic	Anticipation	Considering potential environmental and social implications of biotechnology products is important in the planning stages of research.	There should be a standard of at least 10% of public funding for research in biotechnology that goes to environmental, social, legal, and ethical implications research.
Egalitarian	Responsiveness	The innovation process should respond to changes in public attitudes or values.	The innovation process should respond to changes in public attitudes or values even if this means delaying, modifying or terminating the project.

See text (Methods) for survey questions to assess Deep core beliefs according to Ripberger et al. (2014) using cultural theory archetypes Hierarchical, Individualistic, Fatalistic, or Egalitarian.

agree"). These were subsequently transformed into composite measures as below:

- *Egalitarianism* is the philosophical perspective which emphasizes equality and equal treatment of all people regardless of, religion, economic status, or political belief. People in this worldview seek strong group identities but prefer minimal prescriptions imposed from outside the group (high group, low grid). Consequently, they see value in more collective decision-making. The measures used to create this composite measure were: 1) What society needs is a fairness revolution to make the distribution of goods more equal, 2) Society works best if power is shared equally, and 3) It is our responsibility to reduce the differences in income between the rich and the poor (Ripberger et al., 2014). The three items were averaged to create a single composite measure of egalitarianism where a higher score indicated stronger identification of this philosophical belief (**Table 1**; M = 4.26, SD = 1.36; Cronbach's α= 0.78).
- *Fatalism* is the perspective that people are powerless to influence the future or the consequences of their own actions and that events are determined by fate. People in this group seem themselves as subject to binding external constraints, yet they feel excluded from membership in important social groups (low group, high grid). As a result, they see little control over their lives and that one's fate is much more a matter of chance than choice.

Similar to egalitarianism, we measured this variable asking respondents to identify their agreement with three items: 1) The most important things that take place in life happen by chance, 2) No matter how hard we try, the course of our lives is largely determined by the forces beyond our control, and 3) For the most part, succeeding in life is a matter of chance (Ripberger et al., 2014). From these three questions, we created a composite variable (**Table 1**; M = 3.15, SD = 1.22; Cronbach's α = 0.82) where higher scores indicate stronger fatalistic beliefs.

- The third grouping of cultural worldviews, *hierarchical*, (high group, high grid) reflects high group attachments and binding external prescriptions. Accordingly, they place weight on the welfare of the group yet are keenly aware of whether other individuals are members of their own group. They prefer that organizations and relationships be stratified according to externally defined rules. Hierarchy was similarly measured with three items: 1) The best way to get ahead in life is to work hard and do what you are told to do, 2) Society is in trouble because people do not obey those in authority, and 3) Society would be much better off if we imposed strict and swift punishment on those who break the rules (Ripberger et al., 2014), and from these three, a composite variable was created (**Table 1**; M = 3.06, SD = 1.16; Cronbach's α = 0.73).
- *Individualism* is the philosophical belief that advocates for independence and freedom to promote one's goals and desires over the needs of the group or society. Individualists tend to attach little weight to group affiliation and reject externally defined prescriptions (low group, low grid). We measured individualism with three items: 1) Even if some people are at a disadvantage, it is best for society to let people succeed or fail on their own, 2) Even the disadvantaged should have to make their own way in the world, and 3) We are all better off when we compete as individuals (Ripberger et al., 2014), and also created a composite variable for subsequent use (**Table 1**; M = 3.43, SD = 1.12; Cronbach's α = 0.63).

Dependent Variables

For policy core beliefs and secondary beliefs about RRI, we developed, tested, and administered our own survey questions (Roberts et al., 2020; **Table 2**). Our policy core beliefs questions are based on the general principles of RRI (inclusion, anticipation, responsivity, and reflexivity) from Stilgoe et al. (2013), as they apply to biotechnology innovation as the policy subsystem (Roberts et al., 2020) (**Table 2**). For secondary beliefs, we designed questions to implement RRI principles according to ideas from Stilgoe et al. (2013). These represent specific policy practices that could be taken in biotechnology innovation to implement RRI (**Table 2**). The survey questions in**Table 2** were pre-tested and used in a prior peer-reviewed study that investigated United States biotechnology stakeholder attitudes towards the four tenets of RRI (policy core beliefs) and ways to implement them (secondary beliefs) (Roberts et al., 2020).

Responses to the four questions of RRI policy-core beliefs or to the four questions of RRI secondary beliefs (**Table 2**) were compiled into two separate composite scores, and then each composite score was used as the dependent variable to examine whether demographic, sociographic, and professional factors, or deep-core beliefs from cultural theory (independent variables—**Table 1**) influenced attitudes about RRI principles or practices (**Table 2**). *Responsible Innovation Policy-Core Belief Strength* was measured using a composite from the four items (**Table 2**) (each item on 7-point Likert scale). These items were averaged to form the composite index, with higher scores indicating more agreement with the tenets of responsible innovation (**Table 1**; M = 5.53, SD = 0.92, Cronbach's α = 0.69). *Responsible Innovation secondary beliefs* were similarly measured using four items on 7-point Likert scales (**Table I**). A composite index was created from these items where higher score indicates more agreement with the secondary belief statements (**Table 1**; M = 4.89, SD = 1.26, Cronbach's α = 0.77).

We utilized ordinary least squares (OLS) hierarchical regression modeling, ANOVA, and Chi-squared analysis in SPSS software to test our research questions and explore relationships among the independent and dependent variables as discussed in the Results (*Results*).

Study Limitations

Our study is limited in the number of participants (n = 110) and their geographical location as we sampled from stakeholders in United States biotechnology innovation located in the Research Triangle NC area (as discussed above in *Recruitment and Survey Participants*). Our study is also limited in the design of the survey questions (**Table 2**; *Dependent Variables*). All studies are limited by the choice and number of survey questions, and our study is no exception. When we designed the survey for RRI principles and practices (in 2016), to our knowledge, there were no survey instruments for assessing agreement with RRI in the literature. We focused on Stilgoe et al. (2013) in our survey design as it is the most highly cited paper when one searches for "responsible innovation" in Google Scholar. Specifically, we drew our questions from Stilgoe et al. (2013) textual descriptions of the four elements—anticipation, reflexivity, inclusion, and responsiveness--for the RI principle statements (aka policy core beliefs; **Table 2**) and from their "Indicative techniques and approaches" (Stilgoe et al., 2013, p. 1573) for the questions about secondary beliefs or practices (**Table 2**). We made particular choices for both sets of questions based on our understanding of the RRI literature and experience with the field of science and technology policy and RRI (see also Roberts et al., 2020 for discussion of this limitation). However, across the eight total RRI questions (**Table 2**), we feel the set captures the spirit and expression of RRI as articulated in Stilgoe et al. (2013).

Regardless, other choices could have been made for the survey questions. Thus, our results are constrained by the use of Stilgoe et al. (2013) to derive the principle questions and by our desire to use a reasonable set of questions for implementing RI. We mitigated this limitation by combining four questions into one construct for each dependent variable (8 questions total—4 for policy core beliefs or principles of RRI and four for secondary beliefs or practices of RRI; **Table 2**). We believe this to be a reasonable set for our novel, quantitative exploration of attitudes

TABLE 3 | Quantitative regression model for predicting RRI policy core and secondary beliefs.

		Model 1: RRI policy core beliefs as dependent variable[a]		*Model 2: RRI secondary beliefs as dependent variable*[b]	
	Question	***Stand. β coeff.***	***p-value, sig***	***Stand. β coeff.***	***p-value, sig***
Block 1: Demographics					
	Age	−0.125	*0.324*	−0.104	*0.356*
	Gender	+0.039	*0.706*	+0.081	*0.378*
	White/non-White	−0.155	*0.103*	−0.020	*0.813*
	Incremental R^2 (%)	6.0%		11.7%	
Block 2: Sociographics					
	Highest level of education	+0.165	*0.141*	−0.026	*0.796*
	Annual income	−0.039	*0.703*	+0.033	*0.716*
	Incremental R^2 (%)	8.3%		12.2%	
Block 3: Profession-related					
In what sector do you work?	Industry	−0.676	*0.120*	−0.798[b]	*0.041*[b]
	Academia	−0.501	*0.219*	−0.546	*0.136*
	Government	−0.379	*0.333*	−0.440	*0.210*
	Advocacy	−0.213	*0.542*	−0.329	*0.294*
	Trade	−0.451	*0.232*	−0.662[b]	*0.050*[b]
Length worked in sector	Years in sector	+0.223[a]	*0.073*[a]	+0.007	*0.947*
	Incremental R^2 (%)	18.7%		29.8%	
Block 4: Deep core beliefs					
	Egalitarian	+0.321[c]	*0.006*[c]	+0.360[d]	*0.001*[d]
	Fatalist	−0.054	*0.627*	+0.008	*0.933*
	Hierarchical	−0.090	*0.472*	−0.067	*0.552*
	Individualistic	−0.079	*0.535*	−0.084	*0.461*
	Incremental R^2 (%)	29.6%		43.5%	

Bolded text emphasizes the categories of the analyses.
[a]$p < 0.1$.
[b]$p < 0.05$.
[c]$p < 0.01$.
[d]$p < 0.001$.

towards RRI and their relationships to demographic and cultural factors. In addition, the two 4-question constructs are the same ones used as dependent variables for testing all relationships with the independent variables of demographics, sociographics, affiliations and cultural (core) beliefs, so the comparative results about factors that influence RRI attitudes within this exploratory study are valid.

RESULTS

Regression Model for Factors That Influence RRI Beliefs

To investigate our research questions, we conducted two hierarchical ordinary least squares regression models. Specifically, we asked what demographic, sociographic, professional, and cultural-worldview (deep core beliefs from ACF) factors best explain the variance of observed stakeholder's RRI 1) policy-core beliefs and 2) secondary beliefs? For the regression models, variables were entered into the model according to their assumed causal order by separate blocks and according to our research questions. Control variables (demographic variables) were included in the first block, whereas the second and third blocks were comprised of sociographic variables (educational level, household income) and professional variables (including sector affiliation and length of professional experience). The final fourth block incorporates deep core beliefs from ACF and cultural theory (Ripberger et al., 2014). As the IBM SPPS guide (2009) notes, this form of regression modeling adds these blocks in order to statistically control for the other variables, allowing researchers to evaluate the variables in concert with one another to note if "adding variables significantly improves a model's ability to predict the criterion variable and/or to investigate a moderating effect of a variable."

In **Table 3** below, Model 1 pertains to responsible innovation policy-core beliefs (RRI principles) while Model 2 provides comparison among the same factors with regards to secondary beliefs (RRI practices). The factors tested in Model 1 accounted for 29.6% of the variance in RRI principle beliefs (policy core beliefs), whereas those factors tested in Model 2 explained over 43% of the variance in RRI practice beliefs (secondary beliefs) (**Table 3**).

ACF theory would predict that deep core beliefs influence attitudes towards policy-core beliefs, (in our case RRI principles applied to biotech innovation), and secondary beliefs (in our case RRI practices applied to biotech innovation). In fact, as predicted, in our hierarchical regression models, deep core beliefs significantly influenced both RRI principles (Model 1) and practices (Model 2). However, only one of the four worldviews, egalitarian views, was strongly and positively

associated with stronger agreement with RRI principles (policy-core beliefs) (ß = 0.321, p = 0.006) and practices (secondary beliefs) (ß = 0.360, p = 0.001) while the other three worldviews, fatalism, individualism, and hierarchy, did not display prominent effects on RRI principles or practices. We further evaluate and discuss the role of egalitarian views vs. the other worldviews in subsequent tests below.

Professional sector-affiliation also showed significant correlation with attitudes towards RRI practices (secondary beliefs), although not with RRI principles (policy core beliefs). Participants affiliated with the biotech industry or industry-supportive trade organizations showed significantly lower agreement with the practices of RRI (secondary beliefs) (**Table 3**). Participants who work with trade organizations also held less favorable secondary beliefs and agreed less with RRI practices (ß =*–0.662, p =0.05*). However, the negative effect was even more pronounced for participants working with biotech companies (ß =*–0.798, p = 0.041*).

We also tested stakeholder group differences in RRI beliefs using ANOVA. ANOVA results confirmed the regression results, in that we did not find any significant differences among stakeholder groups regarding policy-core beliefs about RRI (RRI principles) (F = 1.64, p = 0.169), but there were significant differences among stakeholder groups with regard to secondary beliefs about RRI (RRI practices) (F = 6.39, p < 0.001). Industry and trade organizations held significantly more negative attitudes about RRI practices than government, academe, or advocacy groups according to ANOVA. The greatest magnitude difference was between advocacy and trade groups (mean difference = −1.36; p < 0.001) with the difference between advocacy and industry groups a close second (mean difference = −1.32; p < 0.0001). The lowest difference, yet still significant, was between academe and industry (mean difference = −0.83, p < 0.01). There were no significant differences between government, advocacy, and academic groups. These results are consistent with our prior results where a marked difference was found between two factions: industry + trade groups vs. government + advocacy groups, with academics affiliating with either faction depending on the specific facet of RRI (Roberts et al., 2020) (note: this previous work tested the four areas of RRI independently—i.e., inclusion, anticipation, responsivity, and reflexivity—and did not use a composite scale that combines all four like we do in this paper).

From the regression, we also found an association between years of professional experience and positive attitudes towards the principles of RRI (policy core beliefs) (ß = *+0.223, p =0.07*). However, this correlation was not significant for the practices of RRI (secondary beliefs).

In **Figure 3**, we present a visual model summarizing the regression results. In our model, the effect of sector affiliation on RRI secondary beliefs is about twice that of cultural beliefs (−0.798 for industry and −0.662 for trade, vs. +0.369 for egalitarian) (**Figure 3**). We then set out to examine the potential synergies between affiliation with biotech industry and deep core beliefs. Within industry-dominated sectors (industry or industry-supportive trade orgs), we wanted to investigate whether certain deep-core beliefs (i.e., non-egalitarian) could amplify negative RRI attitudes to explain these results. This would indicate both sectoral and cultural factors working together (i.e., not only what you belief, but also where you reside).

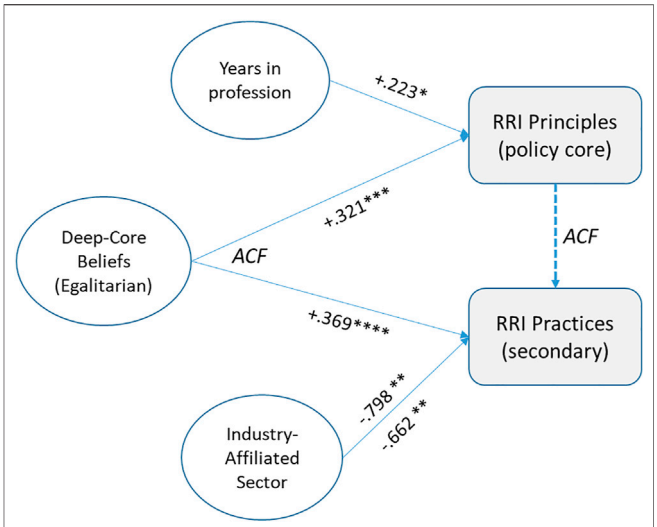

FIGURE 3 | Regression Model for Influencers on Stakeholder Beliefs about RRI in Biotech Innovation. Regression Beta coefficients shown (see also **Table 3**) (p < 0.1*, p < 0.05**, p < 0.01***, p < 0.001****). Industry (company) =–0.798; Trade organization =–0.662. ACF predicts that deep core beliefs influence policy core and secondary beliefs, and that policy core beliefs influence secondary beliefs.

Relationship Between Stakeholder Groups and Cultural Beliefs

An association between a professional sector and certain cultural beliefs (deep core) could help to explain the strong effect on beliefs about RRI practices. If different stakeholder groups hold divergent deep-core beliefs, the ACF predicts that it would be more difficult to form stable policy coalitions transcending stakeholder groups (Jenkins-Smith et al., 2014; Ripberger et al., 2014). In the context of our work, coalitions of stakeholders from different sectors would be more difficult to form and maintain in order to implement RRI if those stakeholders held different cultural world views. To evaluate if different stakeholder groups hold distinct cultural beliefs, we first did descriptive statistics on deep core beliefs (cultural beliefs) by sector (**Table 4**; **Figure 4**). We added up survey responses for each participant from the three 1-7 Likert Scale questions for each cultural archetype (**Table 1**; Methods)—Hierarchical (H), Individualistic (I), Egalitarian (E), Fatalist (F). We then averaged the results for each stakeholder group. The highest possible score would be 21 for each group average (all 7's for the three questions), with the lowest as 3 (all 1s for the three questions). Results are shown in **Table 4**; **Figure 4**. This enables us to evaluate the relationship between these independent variables and also answer if sector affiliation and deep-core beliefs work together to influence attitudes about RRI practices (secondary beliefs). Given the significant positive

TABLE 4 | Deep Core Values by Stakeholder Group--average score.

	Hierarchical	*Egalitarian*	*Fatalistic*	*Individualistic*
Industry	8.3 (3.8)	11.7 (4.0)	9.3 (4.0)	9.7 (3.3)
Academe	9.5 (2.6)	13.2 (3.3)	9.8 (2.9)	9.4 (2.6)
Government	9.1 (4.0)	14.1 (4.5)	9.2 (4.0)	10.0 (3.6)
Advocacy	9.3 (3.2)	13.8 (4.3)	10.8 (3.8)	10.8 (4.3)
Trade	10.2 (3.7)	11.7 (4.2)	8.6 (3.6)	12.1 (2.8)

*Average (std dev) reported. Minimum possible score = 3 and Maximum = 21 given scale of 1–7 for each of three questions in each cultural group (see **Table 1** and Methods).*

relationship between RRI attitudes and egalitarian beliefs and the significant negative relationship between RRI attitudes and industry or trade stakeholder-group affiliation, we wanted to see whether participants from industry and trade organizations scored lower in the egalitarian belief scale.

Although all stakeholder groups scored relatively high on the egalitarian scale (all over 11 points), industry and trade organizations had the two lowest scores (M = 11.7 and M = 11.7). The highest score for trade organizations was in the individualistic category of deep core beliefs (M = 12.1). Individualists tend to hold free-market world views consistent with support of private industry and individual competition in innovation systems (Jenkins-Smith et al., 2014; Ripberger et al., 2014), and the trade representatives came from groups supportive of biotech industry innovation. In contrast, advocacy and government groups held the strongest egalitarian views (**Table 4**; **Figure 4**) (M = 13.8 and M = 14.1 respectively). Thus, according to descriptive statistics, there appeared to be an association between stakeholder group and deep core beliefs that could explain the strong effect on RRI secondary beliefs (**Figure 3**).

We then set out to see if these group differences in cultural world views (deep core beliefs) were statistically significant using Chi-squared analysis. However, we found no statistical differences among stakeholder groups despite the differences we observed in the descriptive statistics (**Figure 4**; **Table 4**). This could likely be due to inadequate statistical power given the low cell size within the cross-tabulated grouping (e.g., n = 16–30) (**Figure 2**). Future work could be done with a higher number of participants in each stakeholder group to see if the lower egalitarianism scores we saw among our trade and industry groups is applicable in the wider United States biotech innovation system.

Other Deep-Core Beliefs and RRI Attitudes

Next, we wanted to determine if other deep core beliefs (cultural beliefs) tended to be associated with attitudes towards RRI. Our regression model showed a strong correlation between egalitarian beliefs and positive attitudes towards RRI practices and principles. But what about the other cultural archetypes? They did not show significance in the regression model, but other variables could have masked their effect. To test if other archetypes of cultural or deep core beliefs relate to RRI attitudes, we split each participant into either a high or low score (relative to the mean) for each of the four cultural archetypes (H, E, I, F). We then conducted two-tailed independent Samples t-tests to determine if these groups differed in their attitudes towards policy core beliefs (RRI principles) or secondary beliefs (RRI practices). In other words, do individuals who are high or low on each cultural deep-core value scale hold distinct policy core or secondary beliefs?

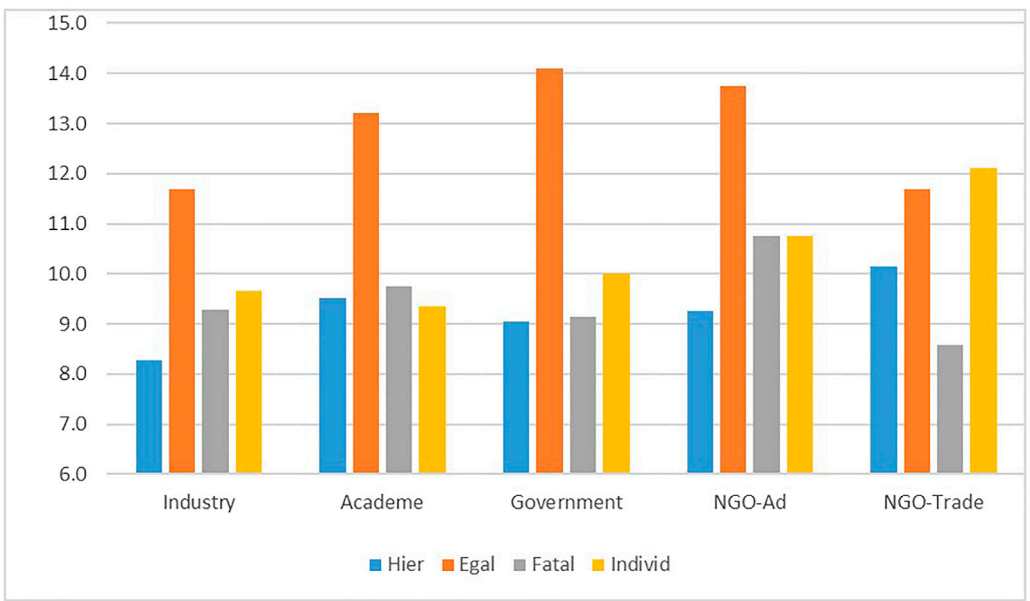

FIGURE 4 | Sectors association with certain deep core beliefs.

TABLE 5 | Deep core beliefs influencing RRI Attitudes.

	RRI principles (policy core beliefs)		RRI practices (secondary beliefs)	
	Mean difference	Sig (2 tailed)	Mean difference	Sig (2 tailed)
Egalitarian	+0.68[a]	0.000	+1.08[a]	0.000
Fatalism	+0.25	0.156	+0.48[b]	0.048
Individualism	−0.47[c]	0.007	−0.75[c]	0.002
Hierarchical	−0.31[d]	0.081	−0.50[b]	0.039

[a]p < *0.001*.
[b]p < *0.05*.
[c]p < *0.01*.
[d]p < *0.1*.

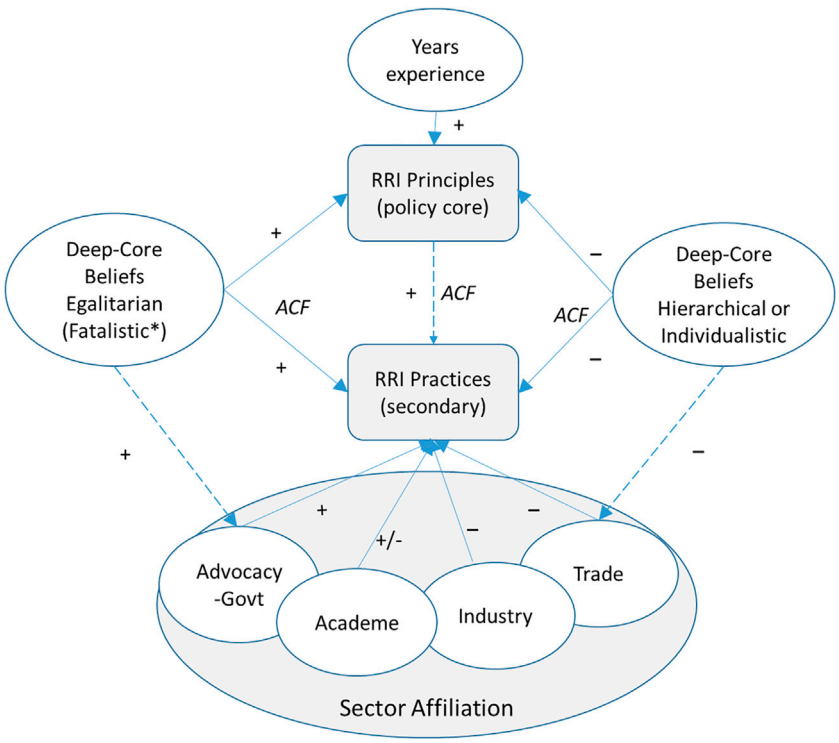

FIGURE 5 | Proposed Model for Factors Influencing RRI Beliefs in Biotechnology Stakeholders. We present this model for further testing and hypothesis building. Plus sign near arrow denotes a positive correlation, minus denotes a negative correlation. Dashed arrows indicate relationships supported by descriptive statistics (between deep-core beliefs and sector affiliation) or ACF theory (between RRI principles and practices). Note that Industry had lower egalitarian views than the sectors to the left in the diagram, but did not have higher hierarchical and individualistic world views than those sectors (see **Figure 4**). *Note also that fatalistic views were statistically significant for RRI secondary beliefs (RRI practices) at $p < 0.05$ and that the positive correlation was also found for RRI policy core beliefs (RRI principles) at $p = 0.156$ although this did not meet our significance criteria (see **Table 5**).

For the policy core beliefs (RRI principles) we found significant relationships with deep-core beliefs for all the cultural archetypes except for fatalism (**Table 5**). For RRI secondary beliefs, we found significant relationships for all of the cultural archetypes (**Table 5**). Egalitarian beliefs continued to have a strong association with positive attitudes towards RRI principles and practices, as confirmed by the regression analysis (**Table 3**; **Figure 3**) and the sample *t*-test (**Table 5**). However, we were also able to uncover through the t-tests that fatalistic beliefs positively influenced beliefs about RRI practices (secondary beliefs) albeit to a lower extent. We were also able to uncover that hierarchical and individualistic beliefs had a statistically-significant negative influence on beliefs about both RRI practices (secondary beliefs) and principles (policy core beliefs) (**Table 5**). We note that this influence is stronger for individualistic world views than for hierarchical world views.

To summarize the results, we expand on our previous model from the regression alone (**Figure 3**) to incorporate the descriptive statistics, ANOVA, and Sample *t*-test results (**Figure 5**). We present **Figure 5** as a hypothesis-generating

exercise, recognizing that our limited study does not confirm these relationships. Larger numbers of stakeholders across wider geographic regions will be needed to do so. Nevertheless, we present novel findings of these empirical relationships that can provide insights into the formulation of attitudes towards RRI policies and practices in United States biotechnology innovation systems. In closing, we now turn to a broader discussion of the model (**Figure 5**) and its potential implications for building cross-stakeholder coalitions to advocate for and implement RRI principles and practices.

DISCUSSION

Our study focused on exploring demographic, sociographic, professional, and cultural factors (deep core beliefs) factors to help explain United States biotechnology stakeholders' attitudes to RRI. In summary, no demographic or sociographic factor was found to have a significant influence on RRI attitudes. However, professional factors of years of experience and affiliation (stakeholder group), as well as cultural or deep-core beliefs, were significant predictors of biotechnology stakeholder attitudes towards RRI. It is important to note that we used study-participants comprised of biotechnology professionals from the greater Raleigh-Durham-Chapel Hill area (Research Triangle, NC). Therefore, our study conclusions are limited to the United States and this region. However, the Research Triangle provides a host of diverse biotechnology and bioscience organizations and is among the most active scientific and development regions in the United States (Rose 2015).

First, we found that those with more years of experience tended to agree more with the principles of RRI. Although we do not know the underlying reasons for this correlation, one hypothesis for our observation is that early biotechnologists experienced public backlash to their work on GMOs (Kuzma 2016; Kuzma et al., 2016; Kuzma 2018), and seeing those conflicts, now want to do a better job of bringing the public into the discussion for this next generation of gene-editing (Kokotovich and Kuzma 2014; Kuzma 2016; Kuzma et al., 2016; Kuzma 2018). Thus, it makes sense that RRI principles like inclusion, anticipation, reflexivity and responsiveness seem to resonate with those who have more experience and lived through earlier biotechnology controversies.

Next, our study is the first to find through quantitative survey research that RRI attitudes, towards both principles and practices, are strongly influenced by deep-core, cultural beliefs. Cultural beliefs have been found to underpin attitudes towards other areas of technology and risk (Douglas and Wildavsky 1982; Jones and Song 2014; Johnson and Swedlow, 2020; Kiss et al., 2020), but to our knowledge, we are the first to report this association in the context of beliefs towards RRI. (**Table 5**; **Figure 5**).

In some ways, the positive association between egalitarian beliefs and favorable RRI attitudes that we discovered is not surprising, given that several concepts of RRI originate from ideas about greater democratic participation in technological decision-making and precaution or humility towards potential technological risk (Stilgoe et al., 2013). Earlier studies find that people who hold egalitarian viewpoints are generally more concerned about technological and environmental risk (e.g., Jones and Song 2014; Johnson and Swedlow, 2020; Kiss et al., 2020), and RRI embraces the principle of anticipating these risks during early phases of research and development. Egalitarian beliefs also include strong feelings of social cohesion and equality among group members, while they eschew authority and role differentiation between group members (Jenkins-Smith et al., 2014). Therefore, egalitarian views resonate with RRI principles and practices of "inclusion" and "responsivity," which strive for an opening-up of innovation systems to the voices and desires of diverse publics.

In contrast, we found that hierarchical deep-core beliefs had a negative influence on RRI attitudes (**Table 5**; **Figure 5**) and these results also make sense theoretically. For example, by definition, hierarchs favor defined roles prescribed by institutions and thus would tend to leave technological decision making to "authorities" or experts with knowledge--these beliefs seem incongruent with RRI's principles and practices related to public inclusion and responsivity in particular. We also saw a negative correlation between individualistic deep-core beliefs and RRI attitudes (**Table 5**; **Figure 5**). Individualists believe in free-marketplaces where people can compete squarely with others, without interference. Individualists may see inclusion or responsivity, and even anticipation or reflexivity, as slowing the pace of innovation or unduly influencing free-market competition. Along these lines, Van Oudheusden (2014) noted the tendency for RRI frameworks to favor social and ethical concerns above economic and free-market concerns. For example, incorporating practices of RRI, such as being responsive to public objections to a biotechnology product or stopping development of it, could prevent the advancement of societally beneficial applications. Van Oudheusden (2014) argued that RRI is not politically or culturally neutral, which is congruent with our results showing the strong association of deep-core (cultural) beliefs with attitudes towards RRI principles and practices.

Although the above findings make theoretical sense, we did not explicitly study underlying motivations as to *why* egalitarians tend to support RRI, or *why* other cultural groups tend to oppose it (hierarchs and individualists). For example, alternative explanations for the association between egalitarianism and favorable RRI attitudes could exist. Egalitarians might have motivations for supporting RRI that relate to a desire to slow innovation given their concerns about risk. For example, in our prior work, we found that biotech developers from industry and academe were concerned about RRI practices delaying innovation (e.g., through public participation or responsive practices), thus decreasing their ability to meet funder's timelines and reducing their competitiveness (Roberts et al., 2020). As egalitarians affiliate with groups often more critical of biotech products (e.g., NGO-advocacy groups), the stalling of innovation could be an underlying motivator for wanting RRI implemented. Future research could investigate the motivations of each cultural group in the context of RRI attitudes, perhaps through qualitative interviews, to better understand the relationships

between cultural-groups, stakeholder-groups, and RRI attitudes that we uncovered in this study.

To our knowledge this is also the first inquiry that uses ACF's three tiers of beliefs (deep-core, policy-core, and secondary beliefs) for exploring the potential for coalitions to form over policies and practices for RRI. For example, ACF posits that if different groups hold divergent deep-core or policy-core beliefs, it is more difficult for them to form stable policy coalitions, as coalitions work together to translate their beliefs into policy action and implementation (which are secondary beliefs) (Jenkins-Smith et al., 2014; Ripberger et al., 2014). We designed our survey of United States biotechnology stakeholders and their RRI attitudes around the three-tier hierarchy of ACF beliefs. We also considered stakeholders' affiliations in our analysis (i.e. industry, trade orgs, academe, government, advocacy groups). Our results showed two primary coalitions that form around secondary beliefs about RRI and deep-core beliefs (more on policy-core beliefs later). One coalition consisted of two stakeholder groups---trade organizations and industry groups. This coalition viewed RRI *practices* (secondary beliefs) less positively. The other coalition consisted of government and advocacy groups and viewed RRI practices more positively (**Table 3**; **Figure 3**; **Table 5**; **Figure 5**). Academics tended to fall somewhere in between (this was also found in our previous study when we surveyed the individual practices of the four elements of RRI--Roberts et al., 2020). The coalition of trade-industry groups also tended to be slightly less egalitarian in cultural world views (deep core beliefs) than government, advocacy, or academic groups according to descriptive statistics (**Figure 4**; **Table 4**). These two major coalitions disagree on RRI implementation in particular. Differences in deep core beliefs and secondary beliefs may work against the possibility that these two coalitions (trade-industry vs. government-advocacy) would form alliances to instill RRI in United States biotechnology innovation systems.

It is important to note that the United States biotechnology innovation system has historically been polarized along stakeholder-group lines similar to the ones we found from the ACF-belief analysis. Industry and trade organizations have been fighting to convince the public and advocacy groups that there are no special risks associated with biotech products (in comparison to conventional or non-biotech products), and therefore, there is no need for people to be concerned about biotechnology risks, labeling of biotech products, or whether regulatory assessments are conducted (Kuzma 2018). In turn, advocacy groups have been fighting for better risk assessments, more transparency, and broader public inclusion in decision-making about biotech products and innovation processes, while challenging government decisions in the courts (Kokotovich and Kuzma, 2014). These two major coalitions have battled for decades for the public's minds and hearts.

On the other hand, we did not find significant differences among United States stakeholder groups with respect to policy-core beliefs, the middle tier of the ACF hierarchy (**Table 3**; **Figure 5**). That is, all stakeholder groups generally agreed on the principles of RRI (**Table 3**; **Figure 5**). The two major coalitions we found seem to differ most with regard to deep-core and secondary beliefs (industry-trade vs. advocacy-government) but not RRI principles or policy-core beliefs. Some possibilities to explain these results come to mind.

One might be that agreement with questions about RRI principles in **Table 2** arose because stakeholder groups or individuals (with potentially divergent deep-core beliefs) subscribe their own meanings to the RRI principles according to their own values or professional position. In other words, the RRI principles may be vague enough for people to interpret them to fit their own world-views. For example, the question for the RRI principle of "inclusion" ("maximizing public participation") (**Table 2**) may be translated by biotechnology developers as unidirectional "public education" or traditional "deficit model" communication (Suldovsky 2016; see also *Previous Work on Biotechnology and RRI*), while social science scholars intend it as deeper public engagement in decision making and giving voice to various publics (Stilgoe et al., 2013). So, it follows when the RRI principles (policy-core beliefs) are translated into more specific RRI practices (secondary beliefs), the industry-trade org coalition cannot sign onto them, and differences in attitudes towards RRI practices are seen between industry-trade and advocacy-government coalitions.

From a more optimistic standpoint, our results indicate that at least historically opposed coalitions can agree on the general principles of RRI applied to biotechnology innovation. Thus, there may be hope for broader coalitions to come together and implement RRI in biotechnology innovation *if suitable practices can be identified for doing so*. Stakeholder coalitions may disagree on secondary values for RRI implementation as we articulated them in this study, but it is possible that other alternatives for RRI implementation could be formulated that would be acceptable across all coalitions and still adhere to the robust version of RRI principles (Stilgoe et al., 2013).

To assess the two possibilities, future studies should bring diverse United States stakeholders together to further discuss their meanings of RRI principles (i.e., what are they reading into statements about RRI principles like the questions in **Table 2**) and articulate a broader range of potential practices for each RRI principle (i.e., what might be alternative practices to those proposed in **Table 2**). RRI practices that respect a range of cultural world views (H, I, E, F), not just egalitarian beliefs, should be considered. Translating or incentivizing RRI practices for hierarchs and individualists will be especially important given their reticence towards the socially equalizing aspects of RRI. This could be a strategy for engaging polarized coalitions in biotechnology innovation, those that may not share deep-core beliefs.

The significant institutional barriers to implementation will also need to be considered, although they are perhaps not completely separable from barriers due to cultural beliefs. Our previous work (Roberts et al., 2020) and the work of other scholars (see *Previous Work on Biotechnology and RRI*) identified barriers to RRI implementation as competition and pressures to move quickly with biotech R&D in light of funding deadlines, needs to publish first, and to gain scarce private investments. Recent work by Wittrock et al. (2021) also found "tensions between excellence criteria, premised on maximizing

grants and publications on the one hand, and making room for adherence to RRI aspects on the other." (p ix). They also theorize that "the RRI model does not fit well with the US's sociotechnical imaginary" of the United States science and technology innovation system which focuses more on governance by market mechanisms (p. 101). Other scholars note that RRI resistance among researchers and innovators is in part due to their feelings that the public does not have the requisite expertise or knowledge and may have irrational fears (Marris et al., 2015; Suldovsky 2016; Hartley et al., 2017).

These previously identified barriers have relationships to our findings about cultural world-views and RRI resistance. For example, those that hold stronger hierarchical views see governance as most-appropriate by top-down expertise and this view relates to deficit-model thinking as a barrier to RRI. Those that hold stronger individualistic cultural beliefs see governance by the free-market as most appropriate, and this view relates to competition for funding and resources as a barrier to RRI. In summation, cultural beliefs color attitudes towards RRI principles and practices, and also point to both attitudinal and institutional barriers.

In conclusion, we present the model in **Figure 5** as hypothesis testing, not confirming, and for future testing. Again, our study was limited in the numbers and geographies of participants in biotechnology innovation, and more statistical studies are needed to determine if United States stakeholder groups really do hold different deep-core beliefs which the ACF would predict to be prohibitive of stable cross-sector coalition formation around RRI. The ACF also hypothesizes that cross-coalition learning and engagement is more likely to occur where discussions focus on secondary beliefs or policy implementation rather than on differences in core beliefs (Weible et al., 2009). Although knowledge of deep-core beliefs is important for predicting long-term coalition formation, it is not as important for temporary associations of coalitions for particular short-term purposes (aka "policy flings" from Lawton and Rudd 2013). Perhaps focusing cross-sector dialogues on RRI implementation (while keeping in mind that there are differences in deep core beliefs) is a better strategy for bringing different biotechnology coalitions together to practice RRI within innovation systems. Future studies may also further the robustness of quantitative work on attitudes towards RRI practices. There is an opportunity to develop and validate a scale which measures RRI practices with greater comprehensiveness and granularity than the composite scale for RRI practices used in this study (**Table 2**; see *Study Limitations*). Surveys with a more expansive set of questions about RRI practices that are administered to a larger, and more diverse set of respondents from a variety of geographic locations, stakeholder affiliations, and science and technology arenas could replicate or expand our findings to build a more significant corpus of theoretical work in this area.

Regardless, it will be a challenge to devise suitable RRI practices that 1) remain true to social science RRI principles (ala Stilgoe et al., 2013); 2) consider institutional barriers that innovators face (Roberts et al., 2020); and 3) respect different deep-core beliefs. Yet, we remain optimistic for RRI implementation given industry desires to better include the public in dialogue about newer gene-editing methods (Kuzma et al., 2016; Center for Food Integrity, 2020), and in light of our findings that historical opponents in the biotechnology policy subsystem agree on the broad principles associated with RRI. Given that the emerging oversight system for gene-edited products in food, agriculture and the environment is lacking in public transparency and engagement in key ways (Kuzma 2018; Jaffe 2019; Kuzma and Grieger 2020), it will be important for United States biotech stakeholders to work across sectors and collaboratively construct principles and practices to be more inclusive and responsive to diverse publics and consumers in order to foster legitimacy and potentially trust. Understanding the perceptions and beliefs towards RRI across stakeholder and cultural groups is a step forward for collaborative governance, along with efforts to overcome some of the attitudinal and institutional barriers as important subsequent steps.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by NC State University Institutional Review Board. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

JK contributed to conception and design of the study and the collection of the data. CC contributed to the conduct of the statistical analyses. JK and CC interpreted the results. JK wrote the first draft of the manuscript. JK and CC wrote sections of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

FUNDING

The research in this paper was supported by United States National Science Foundation grant 1540244. NSF provided funds to conduct the survey work. Open Access publication fees are provided by NC State University to JK.

ACKNOWLEDGMENTS

The authors also appreciate the reviewers for their helpful comments. This study was reviewed by the IRB at NC State and conducted under Protocol #6157 and determined to be Exempt.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Political Science

CONCEPTUAL ANALYSIS
published: 06 September 2021
doi: 10.3389/fpos.2021.745898

Governance Choices of Genome Editing Patents

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There are a variety of governance mechanisms concerning the ownership and use of patents. These include government licenses, compulsory licenses, march-in rights for inventions created with federal funding, government use rights, enforcement restrictions, subject-matter restrictions, and a host of private governance regimes. Each has been discussed in various contexts by scholars and policymakers and some, in some degree, have been employed in different cases at different times. But scholars have yet to explore how each of these choices are subject to—or removed from—democratic control. Assessing the range of democratic implications of these patent governance choices is important in understanding the social and political implications of controversial or wide-ranging technologies because their use has a significant potential to affect the polity. This paper seeks to unpack these concerns for genome editing, such as CRISPR, specifically. Patents covering genome editing make an interesting case because, to date, it appears that the polity is concerned less with certain kinds of access, and more with distribution and limits on the technology's particular uses, such as human enhancement and certain agricultural and environmental applications. Here, we explore what it means for patents to be democratic or non-democratically governed and, in so doing, identify that patents covering many of the most controversial applications—that is, ones most likely to gain public attention—are effectively controlled by either non- or anti-democratic institutions, namely, private restrictions on licensing. This may be effective—for now—but lawmakers should be wary that such restrictions could rapidly reverse themselves. Meanwhile, other choices, like compulsory licenses, more broadly touch on democratic deliberation but, as currently structured, are aimed poorly for particular applications. Insofar as the public wants, or perhaps deserves, a say in the distribution and limits of these applications, illuminating the ways in which these governance choices intersect—or fail to intersect—with democratic institutions is critical. We offer some concluding thoughts about the nature of patents and their relationship with democratic governance as distributed claims to authority, and suggest areas for scholars and policymakers to pay close attention to as the genome editing patent landscape develops.

Keywords: CRISPR, patent, democracy, governance, law

OPEN ACCESS

Edited by:
Michael Morrison,
University of Oxford, United Kingdom

Reviewed by:
Katerina Sideri,
Panteion University, Greece
Florian Rabitz,
Kaunas University of Technology, Lithuania

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

Received: *22 July 2021*
Accepted: *24 August 2021*
Published: *06 September 2021*

Citation:
Scheinerman N and Sherkow JS (2021) Governance Choices of Genome Editing Patents. Front. Polit. Sci. 3:745898. doi: 10.3389/fpos.2021.745898

INTRODUCTION

Few technologies are recognized as revolutionary immediately upon their invention. CRISPR—a form of altering DNA sequences inside living cells, or "genome editing"—stands out among those (Jinek et al., 2012; Gasiunas and Siksnys, 2013). Like other revolutionary technologies, controlling genome editing through typical channels of democracy has been a challenge and a matter of public concern (NASEM Genome Editing Report, 2017; WHO Genome Editing Report, 2021). Patents—legal instruments giving their bearers a right to exclude others from practicing a particular invention—have been proposed as governance tool (Guerrini et al., 2017; Parthasarathy, 2018), but the democratic implications of such a governance mechanism has been largely unexplored. In this paper, we examine patent licensing regimes—laws regarding the limits of how patents can be licensed to others—as a governance mechanism for CRISPR and assess these regimes' democratic implications. While many licensing regimes rely on forms of representative democracy, they also seem amenable to broader forms of participatory democracy, the latter of which may be more effective than omnibus attempts to control a widely distributed technology. Given this, a principal democratic path to controlling genome editing lies in, of all things, patent licensing regimes.

CRISPR is a form of genome editing, the ability to alter the constituent DNA of a living cell (its "genome"), at will using an engineered—and infinitely malleable—bacterial immune system (Jinek et al., 2012; Gasiunas et al., 2012; Cong et al., 2013). It is cheap, easy, and flexible; it has worked in every type of organism yet experimented on (Gustaffson, 2020). But this ease at editing the genome brings with it the potential for societally controversial applications, such as "designer babies" (Greely, 2021). Many of these are, frankly, little more fantasy, but the power of the technology has instilled both awe and fear in the greater public (Maxmen, 2015). Notably, CRISPR is subject to its own body of dystopian literature (Ishiguro, 2021), impressive, given that the technology is not even yet a decade old. And it is has been heralded by one of its inventors as the "holy grail" of molecular biology, a bold statement with few, if any, opponents (Gasiunas and Siksnys, 2013).

As a powerful, commercially valuable technology, CRISPR is subject to a broad patent estate. Foundational patents covering a basic iteration of the technology are owned by the Broad Institute in Cambridge, Massachusetts (a joint effort between MIT and Harvard University) and the University of California, Berkeley, among other collaborating academic institutions (Contreras and Sherkow, 2017). Beyond these patents, there are yet more, held by a variety of academic centers and research institutions around the globe (Egelie et al., 2016). But CRISPR technology is rapidly evolving, encompassing ever broader ways of effectuating genome editing among other applications (Porto et al., 2020; Marzec et al., 2020). The patent estate has similarly evolved (Bire et al., 2021).

While certainly not ignored—and indeed, explicitly mentioned by the WHO's recent report on governing human genome editing (WHO Genome Editing Report, 2021)—patents have largely been overlooked as an instrument of governance of genome editing. This is a somewhat surprising aspect of technology studies scholarship because patents are—if not else—a legal instrument designed to limit the use of a given technology (Boldrin and Levine, 2005). Licenses are permissions to use a patented technology on terms set by patent holder. This means, accordingly, that patents control who can use a given technology, on what terms, where, and when (Guerrini et al., 2017). But not all licenses are mere arms-length agreements among patent holders and interested parties. They are also subject to licensing regimes at the mercy of government and restrictions—beyond simple economic ones—from private parties. On the government side of the ledger, these regimes include government licensing provisions, march-in rights, government-use rights, compulsory licenses, and licensing restrictions. In each of these, and as detailed below, the government either has an interest in the technology to practice it on its own behalf or to compel the patent holder to allow another to practice it in a way government deems fit. Beyond these, private licenses—although there is no requirement to do so—may set ethical conditions on the use of a given technology. This is currently happening for genome editing with the Broad Institute and others imposing ethical licensing restrictions on genome editing, including prohibiting licensees from engaging in some of its more controversial applications (Guerrini et al., 2017).

These licensing regimes—despite all ultimately being forms of technology control—have differing intersections with democratic theory. Some are receptive to the usual instruments of representative democracy, such as the polity's support for research funding for certain applications and not others. Other regimes are one step removed, those where legislative representatives have petitioned patent holders to change their licensing practices. At other end these examples lies private licensing regimes, like those from the Broad Institute, that seem, at first blush, entirely undemocractic. But they are likely similarly receptive to faces of lay, participatory democracy, the populous demanding measures from private actors wielding significant amount of power.

Understanding all of this should be important to theorists and policymakers alike. For theorists, it brings patent licensing as a democratic mechanism of technology control, however successful, to the fore. It also suggests that patent licensing—long thought of as an elitist business—has more nuanced democratic implications, especially for controversial technologies like genome editing. This should similarly be useful to policymakers and advocacy groups seeking legally salient mechanisms to control technology in manners responsive to broader constituencies. This paper examines these features—patentsas technology governance, and patent licensing as democratic instrument—in two parts.

Patents, Patent Licensing, and Technology Governance

Patents as Legal Instruments

Patents are one form, among many, of intellectual property. They are legal instruments that protect inventions from being copied

by others without permission of the patent holder. In this way, patents operate as a right to *exclude* others from making, using, selling, or importing particular inventions (35 U.S.C. § 271(a))—not, as is commonly misunderstood, an affirmative right to use them.

This right to exclude is a limited right and only operates for a limited time: all patents expire, currently 20 years from the date when their underlying applications are filed. While international treaties harmonize a variety of the world's patents laws—including this expiration period (TRIPS Agreement, 1994)—patents are domestic creatures only. US patents, for example, are only enforceable in the United States; UK patents only in the United Kingdom; and so on.

Moving from a patent application to a government-issued patent is nontrivial. Around the world patents undergo a substantive examination to assess whether the claimed invention is worthy of protection. Inventions sought to be patented must meet a variety of statutory requirements; in particular, that the underlying invention is new, useful, and—as the concept is articulated in US law—"nonobvious," i.e., a significant improvement over the prior state of the art (35 U.S.C. § 103). The patent document itself must also properly disclose inventions to the world, broadly enabling those with skill in the art to make and use and invention; describing the invention fully and with particularity; and noting that the invention has some nontrivial use (35 U.S.C. § 112(a)). In addition, patents conclude with claims—single sentence recitations of the underlying invention—that define the specific contours of the patent right (35 U.S.C. § 112(b)). Claims, too, must be sufficiently specific and intelligible to those with skill in the patent's art.

Patents are also not self-enforcing; they must be policed by their owners. This is typically accomplished through litigation, i.e., suits for patent infringement. Generally speaking, an entity infringes a patent where they use the claimed technology in some manner without the permission of the patent holder (35 U.S.C. § 271). The remedy, if there is a finding of infringement, is often either a measure of damages to compensate the patent holder (typically, a royalty) or a court-ordered injunction, stopping the infringer from the accused activity.

Despite these limitations, patents are powerful instruments. Patent infringement, while not a crime, can bring with it serious financial penalties. In the United States, damages for major patent infringement disputes now routinely eclipse $1 billion USD (Kass, 2020). Further, patents' right to exclude may mean that two sets of overlapping patents will block others from practicing a larger invention without an agreement among all relevant patent holders—a case of "blocking patents." Patents are, in effect, legal instruments governing the use of a particular technology (Smith, 2002).

Patent Licensing and Technology Governance

Whatever role patents play in technology development—a hotly contested area of scholarly debate—government policies concerning patent licensing have the potential to ultimately affect access, distribution, and conditions of use on particular technologies. Patent licenses are permissions from patent holders to use a given piece of technology. Like other property rights, patent licenses are subject to a variety of government policies regarding when, whether, and to what extent they can be used. Those policies, the most significant of which are catalogued here, further bring with them important choices about democracy and polity—who, ultimately, has rights to access the technology and under which conditions.[1] For purposes of this paper, we focus less on those decisions as effectuated through substantive patent law—that is, laws concerning which inventions get patented in the first instance, like the nonobviousness requirement—and turn our attention instead to policies surrounding patent licensing and their relationship to democratic or nondemocratic institutions of power. While we focus primarily on United States licensing practices, we note that many of the licensing policies described here have close analogues around the globe—or, in other cases, are harmonized by treaty. Licensing restrictions, potentially more than substantive patent law, have potential to speed or hinder technological development, to place it in the hands of a select few or many, and to decide which applications can be broadly used and under what conditions. Government policies on technology licensing are, too, policies of technological governance and have implications for democratic oversight.

GOVERNMENT LICENSES

Through extramural grants and other programs, governments often fund a substantial amount of research and development within their borders—globally, about $2 trillion USD per year (Sargent, 2020). In the United States, the Bayh-Dole Act allows, but does not require, recipients of certain types of government funding to patent inventions created under their stead. In doing so, however, funding recipients must agree to grant to the United States, a "nonexclusive, nontransferable, irrevocable, paid-up license to practice or have practiced for or on behalf of the United States any subject invention throughout the world" (35 U.S.C. § 202(c) (4)). To be clear, this license applies only to the United States government; the patent holder is free to license—or refuse to license—the patented invention to others. But the Bayh-Dole Act's government license provisions mean, in essence, that the government funding agency can use the patented invention for free. Many countries have similar laws.

Taken broadly, this regime—that public funding grants the government the right to freely use a patented invention—can be construed as a mixed public-private governance mechanism for the development and use of technologies. At the outset, governments must choose which technologies to fund, decisions that are ideally responsive to the desires of the underlying polity. Cancer research, for example, receives a

[1]Although we focus on licensing in this paper, it is also the case that patentability criteria—that is rules regarding which technologies can be patents—similarly involve choices about democracy and polity. That, of course, is a complicated mixture of a variety of branches of government, some of which have more democratic features or procedures than others. For more on this point, see Part B.

substantial amount of government funding because combatting cancer is politically popular (Best, 2012). Picking and choosing which technologies to further develop is then, often, left to groups of independent experts charged with choosing the projects most likely to be successful (Price, 2019). The ultimate technology developed—if anything—is then a product of the funding recipient's own efforts (and, of course, chance). And it is the funding recipient, not the government, that gets to choose whether to patent any resulting inventions or place them in the public domain. In this way, the Bayh-Dole Act its government license provisions control how publicly funded technology is both created and, to a certain degree, disseminated back to the government if not the public writ large.

March-in Rights

Related to the Bayh-Dole Act's government license provisions are the Act's rules regarding "march-in rights." March-in rights allow a government funding agency to "march in" and forcibly grant others a patent license for a funded technology if the funding recipient has not sufficiently commercialized the invention. As set forth in the relevant statute, march-in can occur if the patented invention has not "achieve[d] practical application" or is needed to "alleviate health or safety needs," among other cases (35 U.S.C. § 203(a)). Notably, while threats of exercising march-in rights occur from to time, no U.S. agency has ever formally used the provision (O'Brien, 2013; Thomas, 2016).

Like government licenses, march-in rights, too, can be viewed as a mixed public-private governance mechanism for the distribution of technologies. Again, the public chooses which broader area of technology to fund, while private funding recipients largely direct which implementation of that technology gets developed and whether it will be patented. The benefit of this bargain, in theory, is that the public will have practical, commercial access to the technology, once developed. But where the funding recipient or later patent holder has not commercialized the underlying technology to make it available to the public, government (and, presumably, the polity) has authority to wrest it from private hands. In theory, at least, such governance is a balance between private rights and public benefits from the technology it, itself, has funded. And indeed, recent march-in threats have been couched in just such terms. A 2016 march-in petition directed to the National Institutes of Health and signed by 51 members of Congress requested the agency use its march-in authority "to respond to the soaring cost of pharmaceuticals" by licensing patents "developed with taxpayer funds, [that] are keeping those in need from being able to access care" (Doggett, 2016). March-in, is consequently, a governance mechanism over government funded research "intended to distribute the fruits of those labors to the public" (Thomas, 2016).

GOVERNMENT USE RIGHTS

Apart from licensing those inventions which it funds, the government also possesses the right to use inventions owned and patented by private entities. In the United States, one statute, 28 U.S.C. § 1498(a), allows the government to use or manufacture a patented invention "without license of the owner thereof." Unlike government licenses or march-in rights, however, such a use is not free: the government, after a trial, must pay the patent owner a "reasonable and entire compensation for such use and manufacture." (28 U.S.C. § 1498(a)). This provision, colloquially referred to as § 1498, has, in fact, been used in the United States in the past, most notably, in the late 1950s when the Military Medical Supply Agency used the provision to cut costs on tetracycline, a popular antibiotic, for personnel (Silverman and Lee, 1974). More recently, government threats of using § 1498, have encouraged recalcitrant patent holders to either cut costs in supplying their wares to the government (as with ciproflaxin, the antibiotic used following the 2001 anthrax scare) or enter into other arrangements (as with sofosbuvir, the hepatitis C drug) (Brennan et al., 2016).

Section 1498, consequently, can also be viewed as an instrument of technology governance, a public restriction on private ownership of patented technology. It essentially removes the right of patent holders to forbid the government from using the claimed technology, irrespective of the technology's development history or its genesis from the coffers of government. The public—faced with outsized expenses regarding a particular technology or some other pressing need—can move patented technology from behind private walls into the public sphere, so long as the government pays the patent owner compensation for its use. This larger conflict regarding access to privately owned technology sounds in various aspects of democratic theory concerning the public's right to safety, health, and welfare and its power to use purely private property to effectuate such ends (Smith, 2002).

COMPULSORY LICENSES

Analogous to § 1498, are compulsory patent licenses, the requirement a private patent holder license the claimed technology to another private entity. While compulsory licenses are essentially unheard of in American law, they are well defined by international treaty, such as the 1994 TRIPS Agreement. Compulsory patent licenses have recently been used in Brazil, Ecuador, India, South Africa, and Thailand, among other countries (Thomas, 2014; Resolución No, 2021. LO-001-2021). These licenses have been principally granted to generic drug manufacturers for the purpose of lowering drug costs. In addition, the compulsory license regime contemplated by the TRIPS Agreement has been the subject of some current controversy with respect to patents covering COVID-19 vaccines. The governments of India and South Africa, in particular, have argued that the Agreement's compulsory licensing processes are too lengthy and burdensome to engage in during the COVID-19 pandemic; they have asked the Agreement's oversight body, the World Trade Organization, to waive these (and other) procedures (2 October Waiver Request, 2020). Other countries have followed suit (25 May Waiver Request, 2021).

Compulsory licenses, in this way, present many of the same governance choices as does § 1498, i.e., a public restriction on private ownership of patented technology. While they have largely been used in the public health context—to lower drug costs, for example—compulsory licenses occupy a broader institutional power. They can be used, under article 31 of the TRIPS Agreement, for cases of "national emergency or other circumstances of extreme urgency"—a readily pliable standard. Compulsory licenses are, therefore political choices concerning the distribution of private property in cases of extremis—when too few own too much of a beneficial good, and the government's rights in expanding access. And, like other political choices, they are a resolution a societal tensions between the government's role in respecting private property and democratic process concerning its distribution. One analysis of compulsory patent licenses in Canada—and their diminishment following the North American Free Trade Agreement—characterized this tension in compulsory licenses as just that: between "subjecting domestic law to corporate-led agreements. . .[and] democratic process in Canada" (Mohamed and Chaufan, 2020).

LICENSING RESTRICTIONS

Whereas compulsory licenses allow the government to compel patent license to others—that is, without the permission of the patent-holder—the government also has the power to restrict patent licenses if the underlying license agreements violate public policy. There are a variety of circumstances under which such restrictions arise, although they mainly center on various aspects of promoting market competition. One particularly prevalent example concerns "reverse payment agreements," the practice of patent-holders paying others to take licenses to their technologies, often because the underlying patents are of questionable validity or it is a cost-effective way at keeping others out of the market for a given period of time (FTC v. Actavis, Inc., 2013). There are also restrictions on licensing patents beyond their expiration date (Kimble, 2015 v. Marvel Entertainment, LLC, 2015); licensing patents to cover technology beyond that protected by the patent (Princo Corp. v. ITC, 2010); and licensing patents in a collusive manner (Illinois Tool Works, Inc. v. Independent Ink, Inc., 2006). In the United States, resolving these tensions are difficult, but active policing of licensing restrictions are minimal relative to the quantity of licensing and litigation otherwise present. In Europe, by contrast, it is an active area of public litigation despite the recognition that patent protection is in many ways, itself, anticompetitive (Petit, 2017).

Restrictions on patent licensing govern circumstances under which private agreements regarding access to technology. Unlike some of the other cases described above, these do not immediately concern the public's use of the technology or, as with § 1498 or compulsory licensing, the government picking winners and losers to use technology. Instead, they center on platting a level (and broad) playing field for private participation in a given technology. This is layered on an already substantial literature exploring the relationship between democratic ideals and the antitrust laws. Recently, for example, Lina M. Kahn drew a deep connection between the market power of online platform services, such as Amazon, and their potential to diminish democratic values, even in absence of traditional antitrust concerns like consumer welfare (Kahn, 2017). Patent licensing restrictions, therefore, can be seen as a governance choice—sometimes imbued with democratic ideals—regarding the private development of technologies.

PRIVATE GOVERNANCE REGIMES

Beyond these public patent licensing governance regimes, there is a wealth of private ones. Private patent holders largely possess the right to license their patents to whom they want to on, and on a variety of financial and practical terms. The largest divide, perhaps (at least in terms of access and distribution to a given patented technology) is whether the license is exclusive or nonexclusive—that is, whether the technology will be licensed exclusively to a single other entity or broadly licensed among a variety of market participants. But there are, to be sure, various gradations in between (Graff and Sherkow, 2020).

This right to license brings with it a right to establish licensing conditions governing specific uses or development restrictions over a particular technology, i.e., barring licensees from engaging in particular veins of research or development. This occurred most recently with a suite of genome editing patents owned by the Broad Institute. The Broad Institute, for its patents covering its CRISPR technologies, established a tiered regime system for its licenses concerning whether they were used for academic research, tool development, or commercial products (Contreras and Sherkow, 2017). In addition, the Broad Institute forbid its licensees from engaging in research pertaining to various controversial applications of CRISPR genome engineering, including "gene drives," sterile seed technology, tobacco enhancement, or human germline engineering (Guerrini et al., 2017). Contrapositively, others have pledged not to enforce their patents against others, unless users were engaged in various forms of unethical behavior. This was, perhaps, most famously proposed by the scientist Kevin Esvelt, regarding using CRISPR in an inheritable, "gene drive" form (Parthasarathy, 2018).

These private license restrictions are themselves a form of private governance, here, a profit-seeking company's autonomy to determine how a technology gets developed and on what terms. In some instances, they are commendable and dovetail with governance values centered around attention and expertise. Oftentimes, private licensors are experts in the technology's field and know most about a given technology's societal dangers and technical pitfalls (Guerrini et al., 2017). But such private license regimes can, in many ways, be antidemocratic. They do not, in any appreciable sense, allow the public input in what uses will and will not be restricted. These challenges notions of transparency and legitimacy in technology development. In the words of Shobita Parthasarathy, private patent license regimes "seem ill-equipped to address complex societal and value-based

concerns in an increasingly privatized world" (Parthasarathy, 2018).

CRISPR PATENTS AND TECHNOLOGY GOVERNANCE

The CRISPR Patent Estate

Since CRISPR genome-editing technology was first described in 2012 (Jinek et al., 2012; Gasiunas et al., 2012), governments around the world have issued patents covering various forms of CRISPR-based technology. Arguably, the most famous of these are patents held separately by the Broad Institute and the University of California covering one particular iteration of CRISPR genome-editing, the use of the Cas9 enzyme to cleave a target DNA molecule and a single-guide RNA (sgRNA) to direct Cas9 to its specific, desired location (Contreras and Sherkow, 2017). Those patents have been the subject of a particular contentious patent dispute between the two institutions. In the United States, that dispute continues to rage on, and indeed has grown substantially larger since its inception in 2016. In Europe, the University of California has largely won, with the European Patent Office ruling against the Broad Institute (Zyontz and Pomeroy-Carter, 2021). But there remain persistent disputes pertaining to inventorship over this foundational iteration of the technology.

Beyond these patents, the number of CRISPR patents and patent applications has exploded since the technology's invention. A seminal 2016 paper by Egelie et al. catalogued the patent landscape for CRISPR technologies through 2014, finding hundreds of patent applications distributed across the globe. Since then, others have landscaped CRISPR patents in China, India, and South Africa, among other countries, and reached similar conclusions (Bire et al., 2021; Chowdhury and Gargate, 2021; Naidoo, 2020).

Meanwhile, the CRISPR technology itself has significantly evolved, beyond the Cas9 enzyme and basic forms of genome-editing, to synthetic forms of CRISPR enzymes and powerful, precise applications to make a variety of manipulations to the genome (Porto et al., 2020; Marzec et al., 2020). In addition, CRISPR has been used in ways other than basic genome-editing, including as a disease diagnostic, as a screening tool, and as a guard against deficiencies in other forms of CRISPR (Sanjana, 2017; Chertow, 2018; Zhang et al., 2017;, 2018). All of these variations and uses are likely patent protected in some fashion. A recent analysis by Martin-Laffon et al. (2019) found that 45% of CRISPR patents, worldwide were directed to technical improvements in the field, including the utilization of variants of Cas9, advances in sgRNAs their design, and "multiplexing," making multiple edits simultaneously. At the same time, the reach of CRISPR patents is unevenly distributed by geography, with inventors from the United States and China being—far away—the leading applicants of CRISPR patents (Bire at al., 2021).

There is a strong expectation CRISPR technology will continue to be improved and continue to be patented. The academic literature demonstrates that CRISPR technology will continue evolve; new applications of CRISPR are announced frequently. As a consequence, there will be more patents covering various forms of CRISPR, held by many more players, in more than countries than current patent landscape analyses suggest. Much of this is a consequence of the technology's susceptibility to "democratization," i.e., its ability to be cheap, powerful, flexible, and easy to use (LaManna and Barrangou, 2018). At the same time, various forms of the technology are planned for large-scale commercial develop, which brings with it an increased risk of patent infringement lawsuits. These tensions illuminate how policies concerning CRISPR patents matter both more and less as governance instruments of the technology. While patents covering diverse forms of the technology are increasingly being held by a broader number of researchers and developers, their significance for commercial development means that they are increasingly likely to become arbiters of which variations are likely to be commercially development, who is involved in making such determinations, and how much such development costs. These considerations, in turn, intersect with the technology's relationship with democratic power, institutions, and engagement and participation.

DEMOCRACY AND GOVERNANCE OF CRISPR PATENT LICENSES

Democratic Power and Public Interest

What is democratic governance? What do we mean when we say a government or system is democratic? Defining or identifying key markers of democracy help illuminate its qualities and evaluate how or why its absence is deleterious to society, to the public (as opposed to private) interest, or to general welfare. With respect to the patent licensing as an instrument of governance, two broader principles of democratic theory are worth exploring: The first is an understanding of democracy as an equalizing political power, redistributing power away from elites and toward a greater majority or group (Dahl, 1998). The second is a justification of this governance theory by analyzing its legitimacy (Buchanan, 2002). That is, is there intrinsic value in equitable distribution of political power or do democracies confer certain benefits or impose consequences on the public that makes democracy instrumentally desirable? When it comes to concepts such as equality, for example, many have argued that equality is either ontologically or instrumentally important, or perhaps both (Saffon and Urbinati, 2013). Patent licensing requires policymakers to choose—explicitly or not—whether they (and the polity) prefer outcomes in which benefits are distributed equally themselves or are concentrated only for some, by their users. This suggests an important opportunity and potential for deliberative engagement given that significant priority setting and value creation emerges in these governance choices.

In the case of CRISPR, one of the primary concerns is that its powerful effects will be used to benefit some groups disproportionately and create discriminatory outcomes for others. Patent licenses have the ability to maintain the high cost of therapies, to consequently affect the availability of insurance coverage, and to stymie competition. In addition,

patent licenses often shape which diseases are studied for commercial development (and, therefore, which therapies are available to the public). That is, "it is precisely the novelty and power of CRISPR—and the potential effects of its patent landscape on the public health—that counsel us to solve these problems before it is too late for patients" (Sherkow, 2017). To be clear, this calculus is not different in kind from patent licenses for other therapeutic technologies. But CRISPR's power to treat if not cure a great many unevenly distributed genetic diseases means that the distributional choices made by licensing governance is likely to have an outsized effect on the polity. Governing institutions should therefore be accountable to them. Choosing licensing regimes more (or less) responsive to public input is a choice tied up with varying theories of democratic control of—and equality of access to—novel technology.

Yet this is not to say that such choices should primarily focus on equal access as an end in itself. Given the nature of patent licensing—almost always with at least one private actor involved—these benefits should be primarily evaluated instrumentality. Do they get us what the public wants, even if achieved by private actors? Democracies are not only desirable descriptively, but legitimate insofar as a broader distribution of power creates the conditions for bettering public welfare (Anderson 2009). This may include the public choice to encourage the commercial development of CRISPR for some rarer diseases more so than common ones.

This may have implications for private licensing insofar as greater government reliance on private licensing to regulate technology means that the government becomes more and more accountable to private interests, and less so to the public's interest. This is, in some ways, concerning with respect to ethical licensing restrictions as imposed by the Broad Insitute on its CRISPR patents. Relying too much on this model risks corrupting democratic institutions regarding technology distribution by eroding their ability to distribute resources equitably. In other words, efforts to correct such reliances after the technology has expanded becomes stymied as they become increasingly captured by private interests, giving sway to their desire to earn a profit or thrive above considerations of the public (Carpenter, 2014; Contreras and Sherkow, 2017).

To be clear, these aims are not always at odds. The development of COVID-19 vaccinations, for example, marries aspects of the public interest with government's efforts to distribute novel technology, even while *global* distribution efforts have faltered and remain vastly unequal (Georgieva et al., 2021). And there are pathways in which this can become malicious, such as when government fails to curb the power of technology monopolies and they come to dictate our daily functioning (Kahn, 2017). By giving people greater voice, accountablility, and ability to shape the rules and laws that affect their lives, the polity is better able to advocate against domination and for access, whether it is one desirous of CRISPR therapy or one antagonistic to it (Rahman 2017). With respect to legitimacy, this means the ways in which licensing rules are justified or deemed legitimate depends on whether a particular democratic arrangement of people does well to protect the most vulnerable among us. Majority rule, often considered the default democratic decision-making method, has the capacity to suffer tyrannical tendencies when it comes to just distribution of resources or rights protections—patent licensing or otherwise (Ober 2008). Patent licensing regimes purely dominated by a majority gives the public ineffective recourse when circumstances change.

Democratic Institutions and Mechanisms

Democracies, at their best, equalize political power or, at least, create more equitable systems of power distribution. These can be harnessed toward supporting minority groups, bolstering marginalized populations, and giving agency to those in other vulnerable conditions. But how should democracies arrange their institutions to fulfill these ends in practice? The main theory of democratic institutions borne out of the Enlightenment has been a representative system of governance, one in which we choose the people who choose the laws for us. Some of this justification has been practical: having everyone decide on everything—say, via plebiscite—can prove time consuming and overly laborious. The main substantive reasons though are rooted in a deep distrust of the larger polity to make decisions that foster their own self-determination (Sztompka, 1998). The fear of the unruly mob or the whims of the populous has sustained the ways in which democracies construct institutions around limiting the power of individuals or lay groups. This includes the United States Constitution, which has consistently incorporated a system of sepration of power among the three branches of government, including checks and balances, as a solution to "factionalism" (Federalist No. 10, 1788). Filtering the feelings and views of the public through their representatives has long been seen as an important way to contain the people's unchecked "passions" (Holmes, 1995; Sabl, 2002) while also capturing their principal aims.

And so, too, with governing technology through patent licensing. The bulk of patent licensing regimes readily available are public in nature, with political representatives if not at the helm, accountable to their constituents. March-in rights, government use rights, and compulsory licenses are all effectuated by political actors who—historically at least—wield such power on behalf of (or at least with an ear toward) their constituents. Recent threats of government use rights, for example, were born from the wellspring of constituent demands (Brennan et al., 2016). And yet, not all constituent demands—even popular ones—have achieved changes in patent license objectives. The case of patented AIDS medicines in in the 1980s is notable (Grossman, 2016). So too, perhaps, are patent waivers—thus far not enacted—for COVID-19 therapies and vaccines (2 October Waiver Request, 2020; 25 May Waiver Request, 2021).

Within this context, therefore, it is notable that it is the legislature—rather than, say, an elitist judiciary—that has become the principal site of patent licensing policy and nuance. In the modern age, democratic rule typically means electoral democracy, with the mark of a "healthy" or "stable" democracy one in which there are frequent and fair elections of representatives (Urbinati, 2006). "Mirrored representation"—where representatives who demographically mirror their constituents and can directly attest to their lived

conditions —may even further such governance through patent licensing's instrumental aims (Fishkin, 2013). This theory of a more direct or participatory democracy has particular implications for CRISPR patent licensing governance insofar as it traffics on the technology's use to treat (or "cure") certain forms of disability. Under this theory, the best representative to oversee genome editing patent licenses for a particular condition are those who suffer from the condition themselves. This allows these representatives the knowledge (and political cache) to determine how best to distribute genome editing technologies that can eliminate or modify certain genetic diseases, how such therapies get distributed, and who stands to benefit (or not) from certain forms of access. This removes these decisions from companies in charge of designing such therapies which, while knowledgable about the disease, are more likely moved by market research of demand and principles of profit maximization rather than balancing specific rights of access and advancing societal welfare.

The relationship between profit-maximizing capitalism and representative democracy is comple. While we do not pretend to fully untangle and resolve it here, we do note that patent governance has the potential to be responsive to such democratic interests or remove them from the public entirely. This is analogous, perhaps, to regulatory agencies mandate to protect the public from private interests' cost-cutting, a bulwark protecting safe, reliable, and healthy products for consumption. Increasing the distance from the sight of decision-making runs the risk of making representative legislatures less democratically accountable even as it serves an important function in the system.

DEMOCRATIC ENGAGEMENT AND PARTICIPATION

What role then do or should the populous have in engaging directly in democratic institutions? While there is good precedent in including people through deliberative opportunities in one-off events, what would democratic engagement in patent license governance look like if it were institutionalized? Does this governance construct even make sense given that most people may not even know what patents are, how CRISPR works, or what impacts this intersection may have on their lives?

There are roughly two ways of thinking about public engagement through deliberation: One is through creating or carving out systems of inclusion, such as town halls or participatory budgeting. The other is through allowing groups to participate by creating collective power that acts on institutions from the outside, such as patient advocacy groups that organize to pressure rightsholders to understand their views and push for resources (or object to such work). Beyond these formal collectives, there is renewed interest in creating randomly selected bodies of lay people, like a citizens jury, to assess public perceptions of new technologies (Burgess 2012). If given the right institutional space, resources, and tools—especially in a diverse and well moderated group—these "Citizen Assemblies" have yielded promising results in fostering people's ability to understand and analyze complex problems of technical governance, to interact thoughtfully with one another, and arrive at rights-protecting collective judgments (Farrell, Harris, & Suiter 2019). Recently, they have been used in such places as Scotland, Ireland, France, and Belgium to understand what the people truly want and to experiment with a modified form of direct engagement (Carolan, 2015; McKerrell, 2019, Caluwaerts & Reuchamps, 2014; Fabre et al., 2021). Most recently and relevantly as well, a citizen jury was convened in Austrailia to weigh in human genome editing ("Australia Citizens Jury on Genome Editing, 2021). Conveners of the Australian Citizen Jury aim for a more global event convening paritcipants from around the world to deliberate together (Dryzek et al., 2020).

For genome editing technologies like CRISPR, deliberative forums are likely to include a variety of disability rights groups and environmental protection organizations who are certain to have, for some use cases, diverging views. A number of groups, for example, have advocated for patent holders to turn their attention to particular, oft-neglected diseases, including Duchenne muscular dystrophy (Miller, 2019). Some of this work is encouraged, if not mediated, by major CRISPR patent holders, including the University of California's Innovative Genomics Insttute, 2021. Oppositely, an organized group of citizens in Key West, Florida repeatedly protested against the use of genomically edited mosquitos from being released into the environment, with some early success in halting field trials (Joseph, 2016). As with patented AIDS mediciations, this kind of power—at least in the United States—is a hallmark of democratic governance of technology. Akin to voting, these protections to petition one's government creates conditions for lay people to organize with the goals of either endorsing or protesting technical developments of consequential import.

At the same time, few of these groups or their allies have considered ways in which patent licensing could effectuate their goals, either through representative government or directly, to patent holders. One notable exception is MIT professor Kevin Esvelt's proposal to use patent licensing (and the threat of infringement) to police CRISPR "gene drive" technology—a strategy that has been noted by some advocacy groups (Guerrini et al., 2017). In this way, participatory democracy has an outlet to almost all of the patent licensing regimes above—both those where representative government is the medium through which licensing governance occurs, but also instances of "ethical licensing" by private entities. Further, such licensing governance operates at a scale appropriate and achievable for such groups—retail, condition-by-condition or gene-by-gene advocacy—rather than a wholesale restructuring of the country's technology ecosystem more appropriate for expansive government intervention.

Given these conditions, political theorists interested in using patent licensing as a form of democratic technology governance should consider ways to reduce the democratic deficit of these spaces of power and decision-making authority. And in conjunction, those interested in patent governance should consider ways in which deliberative forums like mini-publics are being included in governance decisions around the world (Dryzek et al., 2020). Including the voice of the people in patent

licensing decisions, both from represented stakeholder groups like the disability rights advocate organizations and in the form of random selection like Citizens Assemblies, can be of incredible importance for the public, affecting upstream moments of private and capital interests as well downstream impacts on the distribution of scarce resources and people's lives. Forgoing such choices leaves participatory democracy to belatedly organize after significant decision making has already occurred.

These kinds of deliberative forums, also known as mini-publics, have varied in kinds, sizes, and selection mechanism and could be convened by institutions responsible for patent licensing decisions, including private entities or, in the case of public licensing, Congress. Similarly, the question of patent governance could included on the agenda of broader deliberative events about technology governance, such as the Australian Citizens Jury. While most mini-publics currently play an advisory role, it is conceivable that, as they gain traction, their instrumental value in risk-governance and modes of engagement becomes more politically acceptable. If licensors grant them increasing levels of authority, they stand to actually impact the law.

Whereas many people consider the lay public less capable of reaching certain decisions on such technical issues, evidence from such mini-publics as Deliberative Polls and other assemblies shows that mini-publics actually have good capacity for learning and understanding technical material, and weighing risk in ways that are helpful value-based perspectives (Fishkin 2019). Given that groups of experts and elites themselves suffer from certain problems of exclusion, such as silo effects and skewed risk assessments, combining experts' work with those from deliberative forums creates the opportunity for greater diversity having in risk assessment and weighing private v. public interests (Scheinerman 2019).

CONCLUSION

Once the province of the arcane, patents should become a larger part of the conversation concerning technology governance, like that surrounding genome editing, for they are a powerful form of technology governance. Licenses, that is, permissions to use patented technologies, determine who, what extent, and under what terms others than can use them. These include a variety of government set licensing regimes that do just that, including licensing regimes sought by the government itself, march-in rights, government-use rights for others' patented technologies, compulsory licenses, and restrictions on licenses, to say nothing of private governance regimes with ethical limitations. These licenses are themselves a form of democratic oversight that gives the public the capacity to preventing purely private interests from superseding their own, especially in ways that are dominating, oppressing, or otherwise harmful or unjust.

These patent licensing regimes also often intersect and have different democratic purchase. Some, like march-in rights, are effectuated only through the filter of representative democracy, and even then are rarely, if ever, acted upon. Others are subject to non or even antidemocratic norms in a variety of exclusionary ways. At the same time, participatory democracy has the potential to shape patent licensing regimes according to popular will (or whim), an effort to control the development and distribution of technology in ways small enough to be effective, both at the level of government, down to individual patent holders.

This a critically important mechanism for a technology like CRISPR, one with such heated public interest and with such intense calls for public accountability. The technology's applications have grown tremendously alongside increased calls for public engagement. There are serious concerns that certain forms of technology, as released to the wider public, will be permanent facets of society foisted on it without its deliberative input. Meanwhile, the CRISPR patent estates, although once held in the hands of few, are rapidly expanding.

Facilitating and incorporating public input for such an expansive technology will likely be a long and difficult task. It is further unclear what, exactly, the public wants for such a wide-ranging technology that has so captured its imagination. Previous efforts, like public commissions, community representatives on government panels, may not be successful to garner a definitive view. Smaller, piecemeal efforts at public engagement over licensing regimes, both public and private, may contribute to better digestible—and more effective—forms of democratic technology governance both because they can be asked a more targeted policy question and because they are situated upstream of further distribution policy questions. Using the patents allows the public to better control technology under currently established legal regimes and do so in a way the public deems equitable. The public is better armed to mitigate the domination of private interests.

Whether this is viable remains to be seen. Scholars should look to see whether patent licensing regimes are, in fact, being used by government to control genome editing technology and whether the public, through the procedures of deliberative or participatory democracy or otherwise, is interested in using patent restrictions as a governance mechanism. Scholars may also further examine licensing restrictions to see what the terms are and how they are generated.

The power of CRISPR, as a technology, ultimately has strongly democratic features insofar as it is the most equitably distributed gene editing tool. It can be used by almost anyone, anywhere in the world, with minimal training and inexpensive reagents. Yet, the technology's commercial development—and some of its most egregious applications, real and, to date, fictional—have sailed over many democractic controls otherwise taken for granted. Democracy, like CRISPR, can be a powerful corrective technology for the ills of society.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

FUNDING

NS was supported by a T32 postdoctoral training grant from the National Human Genome Research Institute to the University of Pennsylvania (T32HG009496).

ACKNOWLEDGMENTS

Thanks to Paul A. Gowder for his encouragement in developing this article, and to Harvard University's Edmond J. Safra Center for Ethics for the authors' opportunity to collaborate on related projects

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Political Science

ORIGINAL RESEARCH
published: 21 September 2021
doi: 10.3389/fpos.2021.731505

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

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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

OPEN ACCESS

Edited by:
Michael Morrison,
University of Oxford, United Kingdom

Reviewed by:
Jane Nielsen,
University of Tasmania, Australia
Katarina Foss-Solbrekk,
University of Oxford, United Kingdom

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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

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 clarifications[1]. 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

[1]The 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-

[2]We 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.

[3]We 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.

[4]Basic, 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 counties 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

[5]Although 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

[6]Benabou 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 Polanía 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

[7]Each 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.

[8]It 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.

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.

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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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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CONCEPTUAL ANALYSIS
published: 22 September 2021
doi: 10.3389/fpos.2021.730869

Public and Stakeholder Engagement in Developing Human Heritable Genome Editing Policies: What Does it Mean and What Should it Mean?

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As scientific research pushes the boundaries of knowledge, new discoveries and technologies often raise ethical and social questions. Public responses vary from surprise, to unrealistic optimism about imminent new treatments, confusion, and absolute opposition. Regardless of the intent, the use of a precise gene editing tool on human embryos, such as CRISPR-Cas9, is an example of such a controversial emerging technology. Substantive disagreement about the appropriate research pathways and permissible clinical applications is to be expected. Many ethical concerns, especially related to genetic manipulation of human embryos, are rooted in deeply held moral, religious, or ideological beliefs that science alone cannot address. Today, more scientists and scientific societies as well as policy makers are calling for public and stakeholder engagement in developing guidelines and policies governing scientific practice. We conducted a critical interpretive review of the literature on public and stakeholder engagement in science policy development regarding emerging technologies to determine the ideals that should guide engagement efforts of entities developing recommendations or guidelines on policy for such technologies. We identify and describe five ideals. To illustrate possible applications of these ideals, we review the engagement efforts described in three reports on heritable human genome editing and assess those efforts in light of these ideals. Finally, we recommend possible avenues for engagement that would advance those goals.

Keywords: genetic engineering, germline modification, heritable human genome editing, science policy, policy and guidelines, public and stakeholder engagement, heritable gene editing

OPEN ACCESS

Edited by:
Michael Morrison,
University of Oxford, United Kingdom

Reviewed by:
Stevienna De Saille,
The University of Sheffield, United Kingdom
Francesco Mureddu,
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Specialty section:
This article was submitted to Politics of Technology, a section of the journal Frontiers in Political Science

Received: *25 June 2021*
Accepted: *08 September 2021*
Published: *22 September 2021*

Citation:
Iltis AS, Hoover S and Matthews KRW (2021) Public and Stakeholder Engagement in Developing Human Heritable Genome Editing Policies: What Does it Mean and What Should it Mean? Front. Polit. Sci. 3:730869. doi: 10.3389/fpos.2021.730869

INTRODUCTION

Scientific research and technology continue to push the boundaries of what we know and what we can do. However, these changes often raise new ethical and social questions. One example is CRISPR-Cas9 and its use in heritable human genome editing (HHGE). While discussions regarding HHGE date back for decades, many were relegated as 'science fiction' due to limitations in technological feasibility (Frankel and Chapman, 2001; Evans, 2002; Dresser, 2004). More common were discussions related to ethical issues associated with clinical uses of genetic technologies, such as gene transfer technology, that was not expected to alter the germline (King and Cohen-Haguenauer, 2008).

In 2012, CRISPR technology was introduced and over the past decade publications and research using CRISPR has exploded (Doudna and Charpentier, 2014; Ledford, 2015). CRISPR is a precise and easy to use gene editing tool which allows for the manipulation of DNA within cells and has potential clinical uses. By 2015, scientists already began publishing research using CRISPR to edit genes in human embryos (Cyranoski and Reardon, 2015; Liang et al., 2015; Ma et al., 2017). Despite the fact that none of the embryos were transferred for gestation, these experiments were controversial and led to substantive disagreements regarding if and how the technology should be used on humans, resulting in calls for additional discussions and international fora and even a call for a moratorium on the research (Baltimore et al., 2015a; Baltimore et al., 2015b; Hurlbut et al., 2015; Kaiser and Normile, 2015; Landphier et al., 2015; Pollack, 2015).

The controversy regarding HHGE came to the forefront of public attention in November 2018 when Chinese scientist HE Jiankui announced that he had used CRISPR to edit a gene in human embryos and transferred them into women, resulting in two twins born in 2018 and a third child born later (Regalado, 2018; Begley and Joseph, 2018). The public seemed shocked by the announcement, which was followed by a flurry of media attention on HE Jiankui, the experiments and anyone associated with them (Regalado, 2018; Begley and Joseph, 2018; Begley, 2018; Begley, 2019; Cohen, 2019). Scientists were also taken aback by the experiments. CRISPR discoverer Jennifer Doudna described being "horrified," United States National Institute of Health (NIH) director Francis Collins found the experiments to be "profoundly disturbing," and Nobel laureate David Baltimore, said it was "a failure of self-regulation by the scientific community" (NASEM, 2019).

These events highlight the need to better understand the public's and stakeholder concerns related to emerging technologies. When scientists move beyond what the public deems acceptable, public backlash can be significant and at times could also undermine research the public otherwise would deem legitimate, such as the use of CRISPR on adult somatic cells which do not contribute to the germline. Following the 2018 incident, many scholars called for further discussions regarding acceptable practices regarding HHGE as well as increased public or stakeholder engagement (PSE) on what research should and should not be conducted (Hurlbut et al., 2018; Saha et al., 2018; Hurlbut, 2019; Lander et al., 2019; Matthews and Iltis, 2019).

Beyond HHGE, calls for PSE linked to science policy development for emerging technologies have arisen in recent years for topics ranging from nanotechnology, human embryo research, and shale gas to vaccine mandates (International Society for Stem Cell Research, 2021; Jones, 2014; Norheim et al., 2021; Pham, 2016; NRC, 2012; NASEM, 2017; North et al., 2014; Jasanoff, 2004; Warnock, 1984). However, it is often unclear what PSE is, what its goals are, how to achieve them, and ultimately how the data collected from PSE can be used effectively to inform policy recommendations and decision making.

PSE is an important part of science policy development, especially when reviewing controversial areas that concern deeply held moral and religious belief and areas where there are significant ambiguities or uncertainties, such as HHGE. Genetic research has had a long history of PSE, especially after the human genome project started and the US NIH began funding ethical, legal and social impact research related genetic research. Understanding patients' and public concerns helps to highlight issues that scientists or physicians may not otherwise address such as the right of access to research findings, equitable representation in research, or determining what is disability versus diversity when viewing genetic differences (McGuire et al., 2020).

In order to successfully develop public policy, PSE must be conducted effectively and thoughtfully, being as inclusive as possible to obtain the often numerous and divergent views found in a pluralistic society. Otherwise, it runs the risk of missing major public questions and concerns or not defining the appropriate issues related to the technology. Ultimately, science policy is implemented by policymakers and not committees issuing recommendations or guidelines. If policy recommendations fail to address public concerns, especially in the United States with polarized politics, they are likely to be ignored or result in unintended limitations to the broader research field.

In this paper, we identify five ideals that should guide PSE efforts when developing science policy recommendations or guidelines on emerging technologies. These ideals emerge from a critical interpretive review of the PSE literature on science policy development, especially those focused on controversial issues. We use these ideals to assess recent engagement efforts described in three seminal reports on human heritable genome editing (HHGE) from the United Kingdom Nuffield Council on Bioethics (NCB), the United States National Academies of Science Engineering and Medicine (NASEM), and the collaboration between NASEM and the United Kingdom Royal Society (NASEM-RS) with an international commission (National Academies of Sciences, Engineering, and Medicine (NASEM), 2020; NASEM, 2017; NCB, 2018). These three reports were selected as they provide the most recent work on HHGE and are used to guide scientific research, especially where local oversight is not robust. The purpose of analyzing these three reports is to illustrate how these five ideals can be understood in practice and used to inform future efforts in the science policy development arena. Reviewing these efforts (and associated public documents), we identify gaps, and recommend improvements that would advance the stated PSE goals from each report. We argue that the efforts made by these three groups, while notable, were not always adequate and more robust PSE efforts are warranted going forward.

DEFINING PSE FOR SCIENCE POLICY DEVELOPMENT

The terms 'public' and 'stakeholder' often are used interchangeably, especially when referring to PSE. However,

they are distinctly different groups in terms of how science policy affects them. For this paper, we use the term 'stakeholders' to refer to "interested or affected parties," who often are organized into groups (North et al., 2014). For HHGE, stakeholders include scientists who conduct the work or are in the broad developmental biology field interested in the results. HHGE stakeholders also include patients and their advocates who believe they or other similarly affected individuals in the future would benefit from gene editing as well as those who donate their gametes or embryos for this research and disability advocates who see genetic variants and "mutations" as forms of human variation that do not need to be "fixed." In addition, stakeholders include those who fund the research (public and private entities), regulate the research, conduct broader social science research on the subject, and hold strong ethical, moral or religious beliefs related to genome editing.

In contrast, we use 'public' as a proxy for the general public who might not have previous knowledge or experience of a topic or are not recognized as specialists (Lezaun and Soneryd, 2007; North et al., 2014; Nuffield Council on Bioethics (NCB), 2012; Reed et al., 2018). Some authors prefer the term 'publics' to avoid the implication that the public is a homogeneous group representing a single set of experiences and perspectives. Our use of the singular is not meant to obscure differences among public perspectives.

Our use of the term PSE, therefore, intentionally covers a broad range of populations. Where there is reason to distinguish between the public and stakeholders, we do so. We hold that including both stakeholders and the public is important in science policy development regarding emerging technologies.

It is important to note what PSE is and what is not. PSE is often confused with public outreach. Outreach is one-way communication with the public. Examples include printed or digital educational materials and lectures open to broad audiences with little to no audience interaction beyond answering a few questions after a presentation. While outreach is important to explain new research and developments in science, it is not PSE. Nevertheless, at times unidirectional communication is erroneously identified as part of PSE.

PSE requires multi-way communication or a dialogue among scientists, stakeholders, and/or the public, such as a presentation of new ideas (a lecture or publication) followed by facilitated discussion. It requires listening and synthesizing outside information, perspectives, and thoughts in the process of developing recommendations or policy (Pieczka and Escobar, 2013). This is especially important regarding developing public policy for controversial issues in science including HHGE.

A wide variety of mechanisms have been used for PSE. Key differences among the mechanisms include whether they are asynchronous or synchronous (live versus recorded), the level of participant activity (from passive to active engagement), who is intentionally included and likely to participate, and whether their primary purpose is to secure consensus or map perspectives and identify issues. Some PSE is invited, through speakers, public comments or calls for information. This is especially common when specific stakeholders and views have been predetermined to be important. Other engagement is more open, allowing uninvited members of the public to share their opinions and perspectives. These exchanges permit those who were missed or overlooked to participate and can remove potential bias that can occur when selecting stakeholders.

Justifications and goals of PSE can inform the design of future efforts and the assessment of past efforts (Stirling, 2012). Some might see PSE instrumentally, as a tool to promote research, dispel myths, or avoid public backlash (National Research Council (NRC), 1996). Some PSE advocates point to the role such efforts play in building trust in science and an appreciation for the legitimacy and importance of scientific research among people with different points of view. PSE may help to secure funding, increase acceptance of results, reduce controversy, and, where relevant, improve adherence to scientific recommendations (Adashi et al., 2020; Kyle and Dodds, 2009; NASEM, 2017; National Academies of Sciences, Engineering, and Medicine (NASEM), 2020; Norheim et al., 2021; NRC, 2012; Pham, 2016). Another reason for PSE is that public involvement in deliberations is required as a matter of principle in a democratic society. Scholars have suggested that people who are affected by a decision should have a fair opportunity to participate in decision-making (Adashi et al., 2020; Kyle and Dodds, 2009; Irwin, 2014; Neuhaus, 2018; Norheim, et al., 2021; National Research Council (NRC), 1996). For others, the primary justification for PSE is that science is public good and a social enterprise that is not only informed and shaped by society but also transforms society (Jasanoff, 2004). Experts from various disciplines are needed to explore the possible implications of scientific developments, particularly as they relate to social and economic effects (Adashi et al., 2020; Nuffield Council on Bioethics (NCB), 2012; van Est, 2011). The public and stakeholders can help to determine how science can most effectively respond to or advance public interests and to make the best decisions possible. Including the public can help identify the challenges to which science should respond and inform the goals of science (Jones, 2014; Barbosa et al., 2020).

Furthermore, science shapes society with the introduction of new knowledge and developments, and with the allocation of social resources used to fund research in lieu of other social goals. In turn, society shapes science by guiding research priorities and establishing regulations and laws that authorize or prohibit different practices (Jones, 2014). For example, the field of global health research emerged after societal pressure and funding from outside of the traditional scientific enterprise, such as the Bill and Melinda Gates Foundation, encouraged researchers to shift their focus (Matthews and Ho, 2008). Understanding science as a public good and social enterprise, a view defended convincingly by numerous science and technology scholars, supports the importance of robust PSE in science policy development. It can improve the quality of scientific research, protect affected parties, and lead to better, more relevant results (NASEM, 2017; National Academies of Sciences, Engineering, and Medicine (NASEM), 2020; NCB, 2018; Norheim et al., 2021; North et al., 2014; NRC, 2012).

TABLE 1 | Embase PSE literature search and results from June 1, 2021.

	Terms	Results
#1	('public engagement'/exp OR 'public engagement') AND policy:jt	79
#2	('public engagement'/exp OR 'public engagement') AND science:jt	194
#3	('stakeholder engagement'/exp OR 'stakeholder engagement') AND science:jt	289
#4	('stakeholder engagement'/exp OR 'stakeholder engagement') AND policy:jt	245
#5	('public engagement'/exp OR 'public engagement') AND emerging:jt	2
#6	('stakeholder engagement'/exp OR 'stakeholder engagement') AND emerging:jt	8
#7	#1 OR #2 OR #3 OR #4 OR #5 OR #6	743

TABLE 2 | PubMed PSE literature search and results from June 1, 2021.

Terms	Results
("technology" [MeSH Terms] OR "technology" [All Fields] OR "technologies" [All Fields] OR "technology s" [All Fields] OR ("emerge" [All Fields] OR "emerged" [All Fields] OR "emergence" [All Fields] OR "emergences" [All Fields] OR "emergencies" [MeSH Terms] OR "emergencies" [All Fields] OR "emergency" [All Fields] OR "emergent" [All Fields] OR "emergently" [All Fields] OR "emergents" [All Fields] OR "emerges" [All Fields] OR "emerging" [All Fields])) AND (("public engagement" [All Fields] AND ("science" [MeSH Terms] OR "science" [All Fields] OR "sciences" [All Fields] OR "science s" [All Fields] OR "sciencing" [All Fields]) AND ("policy" [MeSH Terms] OR "policy" [All Fields] OR "policies" [All Fields] OR "policy s" [All Fields])) OR (("policy" [MeSH Terms] OR "policy" [All Fields] OR "policies" [All Fields] OR "policy s" [All Fields]) AND ("stakeholder engagement" [All Fields] AND ("science" [MeSH Terms] OR "science" [All Fields] OR "sciences" [All Fields] OR "science s" [All Fields] OR "sciencing" [All Fields]))))	267

METHODS

To determine a set of ideals for PSE in science policy, we conducted a critical interpretive review of the literature on PSE in science policy development regarding controversial emerging technologies. The critical interpretive review methodology was developed in bioethics, where the relevant literature comes from multiple disciplines, to capture "key ideas from existing literature" to answer a research question (McDougall 2015, p. 525). We sought to answer the question: What ideals, norms, or principles should guide efforts to engage the public or stakeholders when developing science policy regarding controversial emerging technologies? The critical interpretive review methodology was more appropriate for addressing this question than a systematic review, a methodology designed to capture all relevant studies on an intervention to assess the intervention, because our focus was not comparing the effectiveness of specific PSE approaches or techniques (McDougall, 2015). Our goal was to identify the ideals that should guide PSE processes overall. An additional reason for choosing the critical interpretive review method was that literature from multiple disciplines and different types of publications, including journal articles, reports, and books, would be relevant to answering our research question.

Two authors (KRWM and ASI) manually searched the literature and identified 24 publications for inclusion. A third author (SH) received instruction on data coding, extraction, and reporting, and all three authors read these publications and discussed them to begin to identify themes and inform a more rigorous literature search. One author (ASI) conducted a literature search using embase and PubMed on June 1, 2021. The search terms and results are reported in **Table 1** and **Table 2**. The search resulted in a total of 1,084 publications (743 from embase and 267 from PubMed). The 24 publications identified manually were added to this group for a total of 1,034 publications considered. After duplicates were removed, 988 records remained. ASI screened the titles and abstracts of all records. To be included, publications had to address a controversial emerging technology or the concept of emerging technologies and public policy. They also had to at least implicitly address one or more norms, principles, or ideals that PSE should meet or one or more goals, purposes, or justifications of PSE that could shape our understanding of the principles, norms, or ideals that should inform PSE. Initial review led to exclusion of 819 records. The remaining 145 articles were read and assessed for eligibility. After removing 127 publications, 42 publications remained and were used in answering the research question. All three authors reviewed publications to identify key themes and shared findings using Google Docs. Some publications were read in full by all three authors, some were read in full by two authors, and in a few cases, only one author read the full text. Through critical discussion of the findings, the five ideals discussed below were identified. **Figure 1** reports the search and screening process.

FIVE IDEALS FOR EFFECTIVE PSE

Many scholars have defended the need for PSE and discussed methods for effective PSE (Adashi et al., 2020; Burgess, 2014; Guston, 2014; Jasanoff, 2003 and 2004; Jones, 2014; Kouper, 2010; Kyle and Dodds, 2009; Neuhaus, 2018; Nisbet, 2009; Norheim et al., 2021; Pham, 2016; Pieczka and Escobar, 2013; Selin et al., 2017; Stilgoe et al., 2014; Stix, 2021; Trench, 2006; Varner, 2014;

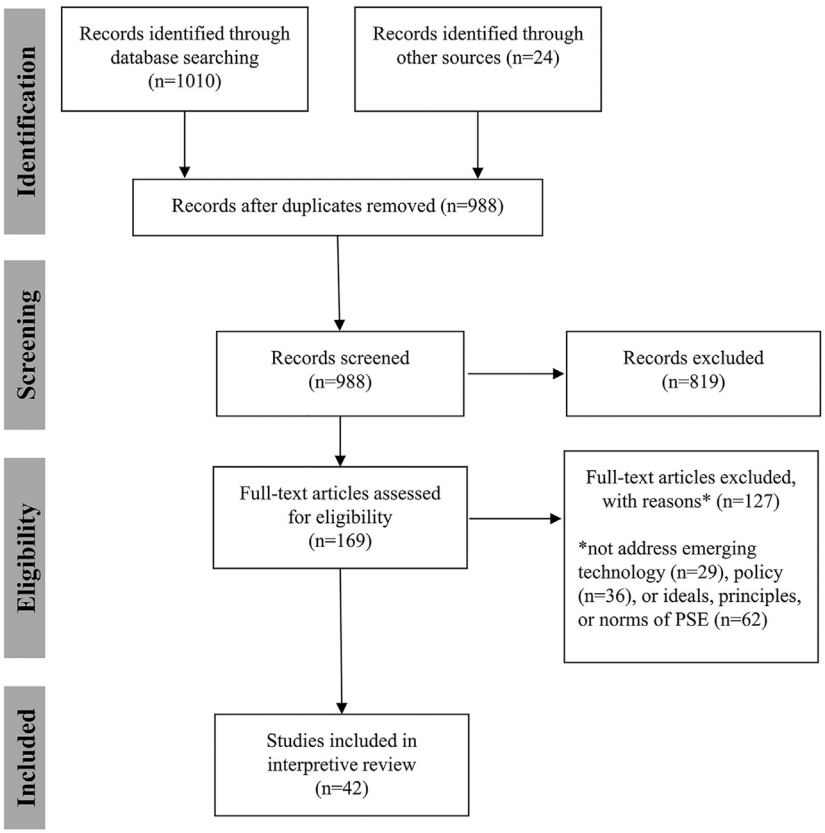

FIGURE 1 | Flow diagram of literature search (based on Moher et al., 2009).

Wilsdon and Willis, 2014). Our analysis of the literature revealed five ideals for effective PSE that should guide committees when conducting assessments and making policy recommendations or decisions regarding emerging, and especially controversial, areas of science research. As defined and described in **Table 3**, PSE should be: 1) comprehensive, 2) transparent, 3) inclusive, 4) methodologically sound, and 5) accountable. These ideals can ensure that PSE improves decision making, especially around controversial emerging technologies, by addressing the right issues and engaging the broadest audience, including marginalized and often missed voices, to improve the quality of decisions and increase trust and legitimacy of guidelines, recommendations, and policies (Norheim et al., 2021). Using these ideals will also allow the resulting recommendations to have a stronger public policy impact, which often relies on, especially in the United States, public approval as many of the policymaker implementing the recommendations are publicly elected.

Unfortunately, many activities labeled as PSE do not accomplish or reflect all five ideals. Some PSE relies on the deficit model, which assumes that members of the public are ignorant and that if they understood the science more fully, they would approve of it (Trench, 2006; Irwin, 2014; Jones, 2014; Simis et al., 2016; NASEM, 2017). This usually leads to unidirectional outreach that consists of experts explaining science rather than true PSE. Such activities fail to meet the goals, justifications, and ideals of PSE, and they do not qualify as PSE as we have defined it.

Other activities capture some of the ideals but not all. For example, common mechanisms employed by the US federal government include issuing notices of proposed new rules in advance with an open-comment period and publishing responses to the comments; live-streaming committee meetings, town hall meetings or other open assemblies (and posting the recording); and developing standing advisory panels that include experts and non-experts (NASEM, 2017; Norheim et al., 2021). These methods can be comprehensive, transparent, and methodologically sound, when properly deployed. However, they have limited inclusion insofar as they only passively seek feedback from the public. There is minimal or no dissemination or push for broad participation as they require the public to be proactive and find the announcements in the public registry on their own. Much of the US government communication also presumes a high literacy level, further limiting participation.

Some PSE models, such as the Expert and Citizen Assessment of Science and Technology (ECAST), serve as better examples (Weller et al., 2021). In an effort to find ways to engage citizen participation to improve science and technology policy, ECAST conducts participatory technology assessments on topics such as biodiversity, climate change, and NASA's asteroid project. Citizen participants identify questions and share feedback on emerging

TABLE 3 | Ideals for effective PSE and their definitions.

Ideal	Definition
Comprehensive	Engagement should begin early in the process of scientific inquiry and prior to technology development, if possible. Public and stakeholder input should inform the questions committees examine and focus on broad questions about the direction of science as well as on particular applications of scientific findings or new technologies
Transparent	All relevant information should be disclosed in a timely and accessible fashion, including: who developed and sponsored the work; who was invited to participate and why they were included; what processes for soliciting feedback were followed; what input was given. Mechanisms should be in place to learn about the meetings, the deliberative process, including disagreements among committee members and unresolved questions, as well as ways to provide uninvited input
Inclusive	Stakeholders and members of the public should be allowed a fair opportunity and encouraged to participate. Information must be communicated in ways that are understandable to people with different levels of literacy and science literacy. People with a broad range of beliefs, perspectives, backgrounds, and experiences should be welcomed and encouraged to participate, including members of groups who have traditionally not been able to participate meaningfully in PSE. Easily accessible mechanisms should be available to provide input, even by people not specifically invited to participate
Methodologically Sound	Engagement should be conducted using evidence-based methods that are aligned to specific project goals or objectives
Accountable	Activities should be assessed using standard metrics to evaluate the extent to which they meet the specified objectives, such as inclusion, and fulfill the other ideals as well as to determine whether the ultimately inform the recommendations developed. This includes documenting processes for receiving and reviewing input. Insofar as some input is dismissed or not incorporated, these decisions should be documented and justified

Sources: Adashi et al., 2020; Barbosa et al., 2020; Burgess, 2014; Cormick, 2009; Fisher, 2011; Guston, 2014; Haywood and Besley, 2014; Heidari et al., 2016; Irwin, 2014; Jones, 2014; Jasanoff, 2003; Jasanoff, 2004; Kyle and Dodds, 2009; Kaner et al., 2014; Kouper, 2010; Lezaun and Soneryd, 2007; Longstaff and Secko, 2016; NASEM, 2017 (p 110, 182); NRC, 2012; Neuhaus, 2018; Nisbe,t 2009; Norheim et al., 2021; North et al., 2014; Nuffield Council on Bioethics(NCB), 2012; Office of Health Equity (OHE), 2019; Pham, 2016; Posner et al., 2016; Reed et al., 2018; Scheufele et al., 2021; Selin et al., 2017; Smith et al., 2021; Stilgoe et al., 2014; Stix, 2021; Stirling, 2008; Stirling, 2012; Stix, 2021; Sturgis, 2014; van Est, 2011; Varner, 2014; Warnock, 1984; Weller et al., 2021; Wilsdon and Willis, 2014.

developments in science and technology, ultimately to help drive more thoughtful policymaking. The model can be comprehensive (participants choose the direction of the discussion and discussions can begin early), transparent, methodologically sound and accountable, allowing one to see what transpired as well as follow up on results. In addition, the organizers make efforts to be inclusive by advertising broadly and encouraging participation from often missed voices.

PSE efforts regarding human embryo research and *in vitro* fertilization (IVF) in the United Kingdom and United States during the 1970s and 1980s also can inform present efforts. They were comprehensive, transparent, inclusive, methodologically sound and accountable. In 1978, the Ethics Advisory Board of the United States Department of Health, Education and Welfare (now the Department of Health and Human Services) was tasked with determining whether IVF and embryo research were ethically acceptable. The board requested comments (written and oral) from stakeholders in various related fields, conducted 11 hearings across the country in nine cities and received more than 2,000 documents which were reviewed by the committee. A similar committee was created to review IVF in the United Kingdom, led by Dame Mary Warnock (Warnock, 1984). The committee spent a year hosting public and private meetings, collecting evidence and opinions from different stakeholder and public perspectives on IVF. After the report was released, the committee gathered additional public feedback (Hammond-Browning, 2015). Both committees developed recommendations, which have lasted for decades, on what types of human embryo research should be permitted. In addition to the recommendations, both also described their deliberation processes. The United Kingdom report, known as the Warnock Report, led to the Human Fertilisation and Embryology Act of 1990 and the creation of the Human Fertilization and Embryology Authority (HFEA) to oversee IVF and human embryo research in the United Kingdom (Matthews and Moralí, 2020). While the United States report did not lead to policy change, it was the first to recommend a limit on human embryo research to 14 days after fertilization, which has been implemented in policies across the world (including the United Kingdom) (Matthews and Moralí, 2020).

For PSE to be successful, it should strive to achieve all five ideals. Time or budget restrictions can make it challenging to fully develop all aspects. But, with advanced planning and some imagination by those organizing the PSE, many, if not all, could be achieved.

PSE FOR HHGE AND PUBLIC POLICY DECISION MAKING

HHGE has the potential to affect all of society and raises a host of ethical issues. Because of the controversial nature of the research as well as its broad social impact for generations, PSE is an important aspect of policy and guideline development. Discussions about the use of gene editing technology are not new, some dating back to the 1960s (Evans 2002; Dresser 2004). Beyond questions related to whether the research ought to be conducted, there has also been discussion regarding which genes should and should not be considered for engineering. These discussions are directly or indirectly influenced by decades-long discussions related to eugenics, once hailed as the key to a healthy population and now condemned (Cavaliere 2018). Because of the nature of this research, scientists have often argued for caution related to HHGE as well as strong policies

TABLE 4 | Statement of PSE in three Reports on HHGE.

Report	Stakeholder and public	Engagement process
NCB (2018) "Genome Editing and Human Reproduction: Social and Ethical Issues."	Reproductive genetics and genomics experts; bioethicists; reproductive and disability rights advocates; and individuals interest in genome editing and human reproduction	Distributed a 27-question survey for professional organizations, stakeholders, and researchers (7 individual and 7 organization responses). Hosted a public 16-question online questionnaire (open for 8 weeks) using Survey Monkey (320 responses) that was reviewed at the Dec 2017 meeting. Organized 3 fact finding meetings (London) with 23 experts in reproductive genetics (6), genomics (9), and bioethics (8). Reviewed notes from 2 previous fact-finding NCB meetings held in 2015 and 2016. Conducted panel interviews of 4 people. Interviewed 6 reproductive and disability rights advocates. Sent the report to 11 external reviewers and integrated their feedback into the final version
NASEM (2017) "Genome Editing: Science, Ethics and Governance"	Affected communities, such as patient groups; companies developing gene editing-based therapeutics; international perspectives on governance of genome editing from permissive, neutral, precautionary, and preventative approaches; and the public	Hosted 4 public meetings (3 in Washington, 1 in Paris) with 37 invited experts, public comment periods and live video streams. Maintained a website with committee and meeting information, videos of past public meetings, an email address for comments, social media feeds and tags, and an email subscription for commission updates
NASEM-RS (2020) "Heritable Human Genome Editing"	Scientists, developers, regulatory bodies, genetic disease patient communities, bioethicists, experts in clinical use, technologies, testing, and animal models related to genome editing; and the public	Hosted 2 public meetings (Washington and London) with 44 invited experts, public comment periods and live video streams. Maintained websites (NASEM and United Kingdom Royal Society) with committee and meeting information and videos of past public meetings, an email address for comments and an email subscription for commission updates. Invited public feedback through a survey in fall 2019 (83 responses). Conducted 4 public webinar lectures, with invited speakers and questions from committee members

to guide the research (Baltimore et al., 2015a; Landphier et al., 2015; Lander et al., 2019).

To address HHGE research and its potential clinical use, three major recent reports assessed the issue and made policy recommendations: the United Kingdom NCB, 2018 report, the United States NASEM, 2017 report, and the 2020 joint report by NASEM and the United Kingdom Royal Society (NASEM-RS) with an international commission. Each report developed a consensus document from a committee that reviewed existing scientific research and knowledge as well ethical and policy challenges. As part of their mandate, each committee indicated that they engaged stakeholders and the public as part of developing their recommendations.

The 2018 NCB report was linked to an earlier NCB assessment of genome editing published in 2016. Both reports were associated with public outcry after the 2015 publication by Chinese scientists using CRISPR to edit human embryos (Cyranoski and Reardon, 2015; Liang et al., 2015). The 2016 report reviewed the current state of gene editing and major concerns across several different fields of research (NCB, 2016). However, the committee determined that HHGE required a detailed assessment of its own. As a result, a second committee was formed, releasing their report in 2018 (NCB, 2018). This committee was guided by a working group with eight members with experience in developmental and cellular biology, law, sociology, and bioethics. As part of their assessment, the committee directed surveys to specific individuals and organizations, conducted a public survey, held fact-finding meetings with experts in associated areas (including developmental biology, law and bioethics), and interviewed reproductive and disability rights advocates (**Table 4**). They also relied on research conducted by the 2016 committee that also included PSE. The final 2018 report as well as associated documents (including survey questions and responses) are available on the NCB public website.

Scientists at the 2015 International Summit on Human Gene Editing called for additional discussions on HHGE, resulting in the 2017 NASEM report (Baltimore et al., 2015b; NASEM, 2017). The committee included 22 members with expertise in basic science, clinical research and medicine, law and regulation, ethics and religion, patient advocacy, and the biomedical industry, with seven members from outside the United States. The group held four public meetings that included public comment sessions (three in Washington, DC and one in Paris), and invited 37 expert speakers (**Table 4**). The final report, committee information, and videos of public hearings are available on the NASEM website.

After the 2018 announcement of the birth of twins with genetically altered DNA at the Second International Summit on Human Genome Editing, there was another international call for renewed discussions regarding the permissibility of HHGE. As a result, the NASEM collaborated with The Royal Society (United Kingdom) to form the "International Commission on the Clinical Use of Human Germline Genome Editing" (National Academies of Sciences, Engineering, and Medicine (NASEM), 2020). This group had 18 members, which included experts in biological science, medicine, ethics, psychology, regulation and law from 10 different countries. They

held two public meetings (Washington, DC and London) with 44 invited experts, four webinars, and hosted a "public call for evidence during fall 2019," which received 83 responses (**Table 4**). The final report, committee information, and videos of public hearings are available on the NASEM website.

In this section, we assess the PSE efforts described in these three reports in light of the five ideals and identify areas for improvement (**Table 3**). Analyzing these reports allows us to not just define the ideals, but to determine how they are or are not used conducting PSE for science policy development for emerging technologies. For the assessment, we reviewed what was discussed specifically within the report and in publicly-accessible materials including (but not limited to) websites, videos of public sessions, and public documents associated with the committee. While each report described some PSE activities and its importance, as illustrated below, the PSE activities reported did not satisfy all five ideals: 1) comprehensive, 2) transparent, 3) inclusive, 4) methodologically sound, and 5) accountable. Entities assigning tasks and charges to committees for science policy should use these ideals in establishing the parameters for committees' work, including allowing sufficient time and resources for effective PSE.

Comprehensive

The ideal of comprehensiveness applies both at a broad level (when and how decision-makers call for PSE) as well as the scope of PSE efforts committees are tasked with (Fisher, 2011; Kyle and Dodds, 2009; Scheufele et al., 2021; Smith et al., 2021; Stix, 2021; van Est, 2011). One measure of the former is how far along research has progressed before PSE begins. Unfortunately, these efforts to develop recommendations regarding HHGE policy in the United States and United Kingdom did not begin until after the 2015 publication reporting the first human embryo to be edited (Cyranoski and Reardon, 2015; Liang et al., 2015). The 2017 NASEM and NCB committees were organized soon afterwards, while NASEM-RS report was a response to the HE Jiankui CRISPR-edited baby announcement (Cohen, 2019). While other policy reports have been produced in the past, all three of the selected reports were started after major research boundaries were crossed. This was not the responsibility of the committees but rather speaks to the failure in the science policy community to address these issues early.

Comprehensiveness also refers to the breadth of the questions and topics considered. Of the three committees, two focused the scope of their work on research governance (NCB and NASEM-RS reports). Notably, they presumed that HHGE would progress and did not seem to consider any possibility of halting it. The NCB committee focused on the nature of the genome and genome interventions relative to other technologies, the obligations of scientists to society, and the principles that should inform legal and regulatory frameworks governing genome editing as well as questions about the application and possible impacts of genome editing. The NASEM-RS committee's charge was to "defin [e] a responsible pathway for clinical use of HHGE, should a decision be made by any nation to permit its use" (NASEM-RS, 2020) The topics covered by the experts were predominantly related to how and for which conditions HHGE could and should be used.

In contrast, the NASEM committee was charged to "examine the scientific underpinnings as well as the clinical, ethical, legal, and social implications of the use of human genome-editing technologies in biomedical research and medicine" (NASEM, 2017). The committee interpreted this charge as excluding most discussions of whether HHGE research ought to be conducted, and focused on issues related to the governance of HHGE. In its final meeting the committee did expand its dialogues to include relevant social considerations, such as what implications the United States' history of race and genetics might have for genome editing and how moral views and public policy are or should be connected. Other ethical and moral questions had little to no discussion. However, in assuming that HHGE research would continue and by limiting discussion to how the research should be conducted rather than remaining open to broader questions about the permissibility of such work, the three committees missed an opportunity to understand why some publics oppose the research. As a result, the recommendations were not responsive to some significant concerns.

Transparent

Transparency is an important part of trust-building for committees reviewing and assessing science policy (Longstaff and Secko, 2016; Norheim et al., 2021; Posner et al., 2016; Wilsdon and Willis, 2014). All three committees' made efforts to be transparent; they developed websites with the charge and purpose of the committee, the meeting schedule, and the final reports; made the working group memberships known; and included lists of experts consulted. The NCB was the only committee to share a public list of the individuals and organizations who submitted comments as wells as the public survey questions, dissemination plan, and results on their website (NCB, 2017; NCB, 2018). The NASEM and NASEM-RS committees held public meetings that were live-streamed with links on their websites for future viewing. The NASEM committee also shared information through social media.

None of the committees adequately explained the methodology used to select experts for input. NCB engaged experts in meetings, surveys, and interviews, but did not explain why particular experts were included in different PSE activities. NASEM-RS had a public survey, but unlike the NCB, they did not publish the survey questions, responses or how the survey was publicized or disseminated in the report or on the websites. While the NCB reported reviewing comments during their eighth meeting, the NASEM and NASEM-RS committees did not mention how or if public comments or survey responses were integrated in their deliberations, only offering that "information provided to the Commission [committee] from outside sources or through online comment is available by request through the National Academie's Public Access Records Office" (NASEM, 2017; National Academies of Sciences, Engineering, and Medicine (NASEM), 2020). After repeated requests for materials, we emailed leadership at the NASEM and received NASEM's information provided to the NASEM and NASEM-RS committees. These materials included

speaker slides from the public sessions, 28 comments sent to the 2017 NASEM committee (via the current projects system), the questions for the NASEM-RS survey and seven invited responses to the NASEM-RS committee. Missing were the public comments received and the online de-identified submissions to the public call for evidence for the NASEM-RS committee.

Inclusive

PSE should seek a broad range of sometimes divergent views and opinions on subjects, including people with different backgrounds, expertise or experiences (Adashi et al., 2020; Barbosa et al., 2020; Cormick, 2009; Fisher, 2011; Heidari et al., 2016; Kyle and Dodds, 2009; Neuhaus, 2018; Scheufele et al., 2021; Smith et al., 2021; Stirling, 2012; Stix, 2021; Sturgis, 2014). Each committee attempted to be inclusive. All three committees included people with expertise in biology, sociology, bioethics and the law; however, the NASEM-RS committee was predominately biologists with only three non-biologists (out of 18 members). To obtain outside perspectives, each committee invited commentary from additional experts, NCB and NASEM-RS conducted public surveys, and NASEM and NASEM-RS held open hearings with public comments sessions and had email addresses publicized for comments. One particularly noticeable omission appears to have been soliciting input from representatives of faith communities.

NCB's survey was sent to several governmental and non-governmental organizations, advocacy groups, and the Royal Society to help publicize it and increase participation. They received 320 responses. In addition, the NCB committee invited feedback on a series of questions from selected groups of stakeholders, obtaining responses from seven individuals and seven organizations. This allowed for diverse voices and opinions to be captured, as seen in their public documents. They made significant efforts to be inclusive.

In contrast, the NASEM and NASEM-RS's PSE activities seemed less inclusive, relying on more passive methods, which made it less likely to have broad participation. Both allowed comments during public sessions, but these sessions were poorly attended, often with only two or three people providing in-person comments and three or four online submitted comments being read or summarized by a committee or staff member. Both committees hosted invited expert speakers. The NASEM committee heard from a few speakers on ethics, focused largely on the United States history of racism and eugenics. Most of the NASEM-RS experts were doctors and scientists (29 of 44) with only three patient advocates. As noted previously, this imbalance suggests that NASEM and the Royal Society saw governance of HHGE their primary focus rather than broader questions about permissibility.

The NASEM-RS committee was geographically diverse and included representatives from 10 countries: Canada, China, France, India, Japan, Malaysia, South Africa, Sweden, the United States and the United Kingdom. The committee PSE included a public survey and four webinars. The webinars only allowed committee members were allowed to ask presenters questions, no public questions although anyone was allowed to watch the webinar. There was limited information on the public survey beyond the questions posed (responses nor demographic information about respondents were included in the public materials NASEM shared). They did note obtaining 83 responses "from every continent and included academic leaders, lawyers, social scientists, philosophers, and representatives from disability advocacy groups, journals, national ethics councils, industry, and scientific societies" (National Academies of Sciences, Engineering, and Medicine (NASEM), 2020). There was no indication that the survey was translated into any other language outside of English. Considering that a goal for the report was for it be adopted globally, making the survey and other materials available in different languages would have made international engagement more meaningful.

Methodologically Sound

PSE activities should be methodologically sound, utilizing evidence-based methods aligned to achieve specific PSE goals (Scheufele et al., 2021). However, none of the reports note why particular methods were adopted. Reviewing other NCB and NASEM reports indicates that the methods chosen are used frequently for reports at NCB and NASEM. NCB often uses similar methods for its reviews: public and stakeholder surveys and interviews, invited experts for comments, and project websites. The 2018 NCB report indicated that there are assessments of these methods during the process, specifically noting that the public survey deadline was extended to advertise it on social media in an effort to increase participation from younger individuals and those with lower educational achievements.

The NASEM and NASEM-RS methods were also consistent with other NASEM projects: project websites, specific email addresses, and recorded open sessions with time for public comments. In fact, both reports used almost identical language to describe their PSE:

The committee's [Commission's] data-gathering meetings provided opportunities for the committee [Commission] to interact with a variety of stakeholders. Each public meeting included a public comment period, in which the committee [Commission] invited input from any interested party. The committee [Commission] also worked to make its activities as transparent and accessible as possible. The study website was updated regularly to reflect the recent and planned [Commission] activities [of the committee]. Study outreach also included a study-specific email address for comments and questions. A subscription to [regular] email updates was available to share further information and solicit additional comments and input to the committee [Commission]. Live video streams with closed captioning were provided throughout the course of the study to allow the opportunity for input from those unable to attend meetings in person . . . [I]nformation provided to the committee [Commission] from outside sources or through the online comment tool is available by request through the National Academie's Public Access Records Office. (NASEM, 2017, p.275-276; NASEM-RS 2020, p.188-189).

While consistency in PSE is encouraging, this near duplication of language in the NASEM-RS and NASEM reports could

indicate that PSE is not as much a priority as a box to check. NASEM is required by United States law some level of transparency and openness in order to be comply with the United States Federal Advisory Committee Act (FACA) guidelines. Some of their PSE can be interpreted as aimed at compliance rather than reflecting a deep commitment to PSE. Moreover, most of the PSE approaches implemented were passive. They posted meetings on their website and expected individuals to find the meetings or calls on their own or come from a pre-identified list of names or emails interested in the topic. They did not indicate any new methods to increase survey or comment participation, nor did, for example, NASEM-RS note reviewing survey responses to ensure broad participation (like NCB did). Furthermore, it is unclear why these PSE mechanisms were used over other widely recommended methods, why surveys were not included in the 2017 NASEM report, or why the NASEM-RS survey had such a poor response (NASEM 2017; Norheim et al., 2021). Different methods likely would have been required to obtain participation from more diverse stakeholders and a broader segment of the public.

Accountable

To be accountable, PSE efforts should include plans for assessment and be assessed both to ensure they are meeting their goals and to measure their impact on recommendations or guidelines issued (Cormick, 2009; Stilgoe et al., 2014; Heidari et al., 2016; Longstaff and Secko, 2016; Selin et al., 2017; Neuhaus, 2018; Scheufele et al., 2021; Stix, 2021). This includes evaluating whether a committee was successful in meeting the other four ideals (comprehensive, transparent, inclusive, and methodologically sound): did they addressed the range of relevant questions and issues, operated and reported their work transparently, reached a broad range of stakeholders and members of the public, and adopted methods that were suited to particular goals? Further, if they failed to meet all ideals, where their reasons and rationales for doing so?

Accountability also means determining the extent to which PSE activities and the information gleaned through those efforts helped shape the recommendations or guidance. If PSE is conducted effectively and integrated within the committee deliberations, the policy recommendations should reflect public and stakeholder input, making it more likely that they will be actionable for policy makers. Policy makers, especially elected policy makers that rely on public support and votes, are often less likely to adopt recommendations that do not adequately reflect public and stakeholder priorities and concerns.

CONCLUSION

PSE is an important part of policymaking for science and technology research and development (Jones, 2014; Posner et al., 2016). As the public are often both the funders and the users of the products of research, their participation in goal setting and establishing research boundaries is vital for science policy to serve public interests and for the public to accept and support emerging research.

Assessing three reports related to HHGE based on the five ideals of PSE—comprehensiveness, transparency, inclusiveness, methodological soundness, and accountability—we found some successes and failures. Deadlines likely limited the PSE efforts each committee could undertake. On average, each committee had less than a year to complete the projects. This timeline was extremely ambitious considering the committees hosted multiple meetings, conducted surveys, collected data, reviewed relevant literature, developed recommendations, and wrote a consensus report.

Often PSE is approached from the perspective that if one explains science effectively enough, then the public will approve of it. As a result, skepticism or questions regarding research are often viewed and labeled as anti-science, even if they do not challenge scientific knowledge (Stirling, 2008). Public discussions also make some scientists uncomfortable when they project the future trajectory of technology and consider possible long-range applications that scientists cannot predict (Stirling, 2008; Jones, 2014). These discussions can get complicated and result in recommendations that the research community does not want because they restrict basic research. For the case of HHGE, public dialogues could find a public uninterested in pursuing the technology at this time, perhaps prematurely limiting research, from the scientists' perspective. On the contrary, PSE could help clarify concerns regarding research to promote alternatives or compromises.

Ultimately, to be effective at PSE for science policy development, institutions performing it must continue to assess and learn new ways to better engage with broader audiences. Guidance from other fields, including public health and business administration, already exists to advise approaches to community engagement for implementing better decision-making processes (Kaner et al., 2014; Office of Health Equity (OHE), 2019). Additional PSE methods could be used to increase inclusiveness including focus groups, Delphi groups, town meetings in various cities (especially those further and less accessible to major policy centers), surveys, and webinars with public questions and surveying. These methods also require effective communication and advertising to the public to encourage participation, using traditional and social media and strategies to include under-represented or marginalized communities. New tools and technologies are constantly being developed that can help scientists and scholars engage more effectively and be more inclusive. It is up to institutions to continue to test PSE models to determine the most appropriate methods for their tasks or charges. There are always lessons to be learned from previous efforts and improvements can always be made.

There have also been calls to move PSE upstream, to begin when new research and technologies are being explored instead of waiting for them to be ready to implement or at least substantially developed, allowing the engagement to be more comprehensive (Jones, 2014). Doing this might require a more formal institutionalized system of PSE, as recommended by the NCB and others (Guston, 2014; NCB, 2018).

Beyond PSE evaluation, entities producing public policy recommendations or issuing guidance scientific research

should evaluate other earlier processes used to develop reports to make their work more effective. For instance, lessons can be learned from the NASEM, 2017 report concerning the need to avoid ambiguity and offer clear, specific and actionable guidance. As noted in their report, NASEM's recommendations were intentionally vague in defining what HHGE should and should not be done:

It is important to note that such concepts as "reasonable alternatives" and "serious disease or condition" embedded in these criteria are necessarily vague. Different societies will interpret these concepts in the context of their diverse historical, cultural, and social characteristics, taking into account input from their publics and their relevant regulatory authorities. Likewise, physicians and patients will interpret them in light of the specifics of individual cases for which germline genome editing may be considered as a possible option. (NASEM, 2017, p. 8, p. 8).

As a result, the Chinese scientist HE Jiankui and his colleagues misinterpreted the recommendations. They believed their experiments to genetically modified human embryos, which resulted in three live births, were justified and consistent with these recommendations (Begley, 2018; Begley and Joseph, 2018; Cohen, 2019). HIV/AIDS is considered a serious disease or condition and the gene HE Jiankui mutated, CCR5, is linked to increased resistance to HIV. The couples targeted by HE Jiankui had HIV + men. While IVF with sperm washing can be used to avoid transmitting the virus in such cases, Chinese law prohibits IVF for individuals with HIV. HE Jiankui offered IVF with sperm washing to couples who would participate in his experiment aimed at making the future children resistant to HIV. HE Jiankui and his colleagues appear to have reasoned that, in the Chinese context, editing embryos to prevent a serious disease was justified since there were no "reasonable alternatives" for these couples. It is unclear whether the NASEM committee members foresaw that their guidelines might be interpreted in this way. Furthermore, after HE Jiankui's experiments were made public, two committee members, Sharon Terry and Luigi Naldini, joined a group of scientists who suggested that the committee's 2017 recommendations were insufficient and endorsed having a moratorium on HHGE (Lander et al., 2019). The NASEM-RS committee was formed to clarify HHGE recommendations and guidelines, suggesting the 2017 recommendations did not provide effective guidance.

These lessons suggest that to best determine the appropriate policies for research in HHGE, more inclusive and comprehensive PSE is urgently needed. While the three reports on HHGE did a good job gauging interest and concerns from vest stakeholders, there is still a need for meaning engagement with the broader public (Jasanoff and Hurlbut 2018). This public engagement should also allow for diverse opinions and questions regarding the goal and products of the work being analyzed. Only with thoughtful engagement and a continued willingness to examine and learn from the past are we likely to see a policy developed that is respectful of the publics it is serving and effective at guiding science.

AUTHOR CONTRIBUTIONS

AI and KM developed the concept of the article and both contributed to the developing the draft. AI conducted the literature review and screened publications. SH reviewed selected literature, highlighted relevant passages within reports for consideration in conceptualizing and assessing public and stakeholder engagement, and formatted references. All authors reviewed and edited the final manuscript.

ACKNOWLEDGMENTS

The authors would also like to thank Daniel Moralí for Rice University's Baker Institute for Public Policy for his help reviewing and proof-reading the manuscript.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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frontiers in Political Science

SYSTEMATIC REVIEW
published: 15 October 2021
doi: 10.3389/fpos.2021.747838

Integrating Public Participation, Transparency and Accountability Into Governance of Marketing Authorisation for Genome Editing Products

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Public participation, transparency and accountability are three of the pillars of good governance. These pillars become particularly important for innovative, personalised health technologies, because of the tendency of these technologies to raise distinct scientific, ethical, legal and social issues. Genome editing is perhaps the most personal of all innovative health technologies, involving precise modifications to an individual's genome. This article focuses on the adequacy of current requirements for public participation, transparency and accountability in the governance of the market authorisation for genome edited products. Although clinical trials for genome edited products are only just underway, lessons can be drawn from the marketing approvals pathways for related gene therapy products. This article provides a broad overview of the regulatory pathways that have been adopted by the US Food and Drugs Administration, the European Medicines Authority, and the Australian Therapeutic Goods Administration for reviewing gene therapy products for marketing approval. This analysis focuses on the extent to which public participation processes and transparency and accountability of review pathways are incorporated into marketing approval policy and practice. Following this review, the article proposes the application of Sheila Jasanoff's "technologies of humility" as a foundation for meaningfully incorporating these pillars of good governance into regulatory processes for the review of products of genome editing. We conclude by articulating clear mechanisms for operationalising technologies of humility in the context of public participation, transparency and accountability, providing a blueprint for future policy development.

Keywords: genome editing, public participation, transparency, accountability, marketing approvals, gene therapy

OPEN ACCESS

Edited by:
Alberto Asquer,
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Reviewed by:
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The Lisbon Council for Economic Competitiveness and Social Renewal,
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Specialty section:
This article was submitted to Politics of Technology, a section of the journal Frontiers in Political Science

Received: *26 July 2021*
Accepted: *23 September 2021*
Published: *15 October 2021*

Citation:
Nielsen J, Eckstein L, Nicol D and Stewart C (2021) Integrating Public Participation, Transparency and Accountability Into Governance of Marketing Authorisation for Genome Editing Products. Front. Polit. Sci. 3:747838. doi: 10.3389/fpos.2021.747838

INTRODUCTION

Public participation is increasingly expected as a core pillar of good governance, along with transparency and accountability, in such diverse contexts as international development assistance (Carothers and Brechenmacher, 2014), human rights (United Nations, 2007), and genome editing (Expert Advisory Committee on Developing Global Standards for Governance

and Oversight of Human Genome Editing, 2021a). Appropriate attention to these three pillars of good governance should lead to higher levels of public trust and confidence, both in the subject matter being governed and in the governance regime itself. In the context of new technologies, particularly those with uncertain risks and benefits, calls for greater public participation, in one form or another, have become *de rigeur*.

The numerous examinations of the complex policy issues associated with human genome editing are a case in point, routinely ending with a call for some form of public engagement, as demonstrated in a report by the International Commission on the Clinical Use of Human Germline Genome Editing (International Commission on the Clinical Use of Human Germline Genome Editing, 2020). A 2017 Report by the US-based National Academies of Sciences, Engineering, and Medicine similarly recognised the need for public participation in the context of genome editing, calling for meaningful public input into the policy-making process. The Report emphasises that public involvement must go further than mere information sharing (National Academies of Sciences, Engineering, and Medicine, 2017, 167). Rather, public involvement should be extended to embrace more active forms of consultation and participation in policy setting and development.

More recently, the World Health Organisation (WHO) Expert Advisory Committee on Developing Global Standards for Governance and Oversight of Human Genome Editing handed down a set of three reports on the governance of genome editing: Governance Framework, Recommendations and Position Paper (Expert Advisory Committee on Developing Global Standards for Governance and Oversight of Human Genome Editing, 2021a; Expert Advisory Committee on Developing Global Standards for Governance and Oversight of Human Genome Editing, 2021b; Expert Advisory Committee on Developing Global Standards for Governance and Oversight of Human Genome Editing, 2021c). The Committee was established in 2018, with the purpose of providing advice and recommendations on appropriate institutional, national, regional and global governance mechanisms for human genome editing.

Two recommendations are particularly pertinent. Recommendation 2 calls for the establishment of a global genome editing clinical trials registry. The Recommendations Report states that making information on clinical trials involving human genome editing publicly accessible reflects the values and principles of openness, transparency, honesty and accountability (Expert Advisory Committee on Developing Global Standards for Governance and Oversight of Human Genome Editing, 2021c, 8). Adoption of this recommendation would thus be an important step in embedding transparency and accountability into the governance of genome editing. Recommendation 7 recognises the critical importance of education, engagement and empowerment. However, this recommendation does not provide the same concrete guidance in how to embed public participation in the governance of genome editing as Recommendation 2 did for transparency and accountability. Rather, the Recommendations Report states that "it would be counter-productive to be too prescriptive on how to pursue education, engagement and empowerment activities" (Expert Advisory Committee on Developing Global Standards for Governance and Oversight of Human Genome Editing, 2021c, 17).

Beyond these exhortations for greater public involvement, little or no guidance has been provided on how to actually engage with members of the public, at what stage and to what end. More specifically, the extent to which regulatory decision-makers considering applications for marketing approvals of new genome editing products should incorporate public involvement is unclear. This is the case whether we are talking about involvement in policy development or more direct participation in the approval process. This article explores the latter, focusing on what best practice public involvement might look like within the specific context of market authorisation for health-related genome editing products.

Market authorisation of the clinical products of genome editing provides a relevant case study for a number of reasons, including: the speed with which the technology has been adopted across the healthcare sector; the relative ease of use of genome editing tools such as Clustered Regularly Interspersed Short Palindromic Repeats (CRISPR); the currently uncertain risks and benefits of healthcare-related genome editing products; the additional normative dimensions relating to heritable genomic changes, including potential inter-generational effects; and the fact that genome editing is often directed towards rare diseases, that by definition will have a smaller evidence base on which regulatory decisions can be made.

In this article we begin with an examination of the current state of genome editing, and provide a review of literature on the core concepts of public participation, transparency and accountability. We then consider the application of these pillars of governance in several jurisdictions, notably the United States, the European Union, and Australia. Specifically, we analyse whether they can be said to be evident in decision-making in relation to gene therapies, which provide some guidance as to the regulatory approach that is likely to be adopted in relation to genome editing technologies. Finally, we discuss the notion of good governance in light of Sheila Jasanoff's work on technologies of humility (Jasanoff, 2003; Jasanoff, 2012), before presenting some initial ideas as to how we might optimise public trust in genome editing regulation moving forward.

WHY GENOME EDITING?

The term "genome editing" embraces a number of important technological breakthroughs which have emerged in the past decade (Gaj et al., 2013). The adaptation of naturally occurring CRISPR and CRISPR-associated (Cas) systems in bacteria for use in mammalian cells is particularly notable (Mei et al., 2016). CRISPR technology is widely seen as being as transformative in the laboratory as the polymerase chain reaction (PCR) was in the 1980s. PCR facilitates rapid multiplication of DNA strands, and is used widely in modern genomic analysis, in both research and diagnosis. Interestingly, though, PCR is currently either being replaced by or combined with CRISPR technology, particularly in COVID-19 diagnosis (Palaz et al., 2021). In much the same way

that PCR was rapidly adopted in the 1980s, it seems that practically every genomics laboratory now has one or more members of the team who is skilled in the use of CRISPR technology. Although only just entering the clinical trial phase, CRISPR-Cas systems and other genome editing technologies have potential clinical application in the treatment of cancer, metabolic disorders, viral diseases, and a large range of other diseases (Li et al., 2020).

Genome editing will clearly be beneficial if it facilitates safe and effective treatment of otherwise untreatable or difficult to treat diseases (Maeder and Gersbach, 2016). The 2017 report by the US National Academy of Sciences and the National Academy of Medicine mentioned in the introduction to this article endorsed the clinical application of genome editing, noting further that the regulatory requirements for assessment of genome editing clinical trials are similar to those for other medical therapies (National Academies of Sciences, Engineering, and Medicine, 2017).

While this appraisal of the apparent ease with which clinical translation of non-heritable genome editing can be assessed within existing regulatory frameworks is encouraging, it understates the challenges involved in navigating the path from laboratory to clinic (Nicol et al., 2017). There is a pressing need to dissect and critically analyze the relevance and adequacy of current regulatory oversight for safely translating genome editing technology into the clinic. This is important because, while insufficient oversight can undermine patient safety, thereby resulting in unnecessary morbidity and mortality, undue regulatory burdens can impede innovation and associated health and economic benefits.

Countries with well-developed health systems have a range of processes for reviewing and approving clinical applications of emerging technologies, generally linked to authority to supply an unapproved medical product or to seek approval for marketing of new medical products (Isasi et al., 2016). One difficulty in the present context, however, is that novel, disruptive therapeutics like genome editing often involve considerable uncertainty about the risks and potential benefits of their use. In particular, the evidence base concerning long-term outcomes tends to be limited. Given the normative nature of risks and benefits, this creates a regulatory pathway that is challenging for regulatory agencies to navigate relying on expert judgement alone (Eckstein, 2015).

Assessments of clinical applications of genome editing present an opportunity to engage a wider range of stakeholders, especially patients and patient groups, in determining the acceptable thresholds for risk and benefits. Ideally, this means not only considering what magnitude of risks are acceptable, but discussing which outcomes are taken into consideration, what counts as harm or benefit, and to whom. More explicit articulation of these risk and benefit tradeoffs, together with the provision of more opportunities for public deliberation about them, makes for a more open, and more democratically and socially robust mode of governance for new technologies.

PUBLIC PARTICIPATION, TRANSPARENCY AND ACCOUNTABILITY IN REGULATORY DECISION-MAKING

Public participation, transparency and accountability may occur throughout the regulatory pathway. Collectively, they can play an important role in policy development and policy agenda setting, but there are also calls for these principles to be applied to the regulatory decision-making process itself (Joss, 1999). This will require decision makers to include considerations extending beyond scientific assessment alone (Taylor, 2021). To fully understand how public participation, transparency and accountability may be utilised in regulatory decision-making generally, and decision-making about genome editing products specifically, it is first necessary to explore the key features of each of these aspects of public involvement.

Why Public Participation?

Public participation involves the "direct participation by non-governmental actors in decision making" (Mostert, 2003, 180). Public participation is widely seen as crucial in advancing the three key cornerstones of democracy: effectiveness, legitimacy and social justice (Fung, 2015). Interest in public participation first gained traction in the 1960s (Arnstein, 1969; Quick and Bryson, 2016). In following years, public participation was incorporated, in one form or another, into various aspects of government decision-making. According to Quick and Bryson, it had become routine and professionalised by the early 2000s (Quick and Bryson, 2016).

The ways in which public participation is incorporated in regulatory policy setting and decision-making continue to be many and varied. Rowe and Frewer have compiled a non-exhaustive list of no fewer than 100 public participation mechanisms which they categorise into three broad types: public communication, public consultation and public participation proper (Rowe and Frewer, 2005). At the most basic level, *public communication* involves the transmission of information from the regulator to members of the public and from members of the public to the regulator in a process initiated by the regulator (Rowe and Frewer, 2005). This process is aimed at gaining information on public viewpoints, but it falls short of true public participation. *Public participation* involves an active process of information exchange, discussion and consensus building, through which more meaningful public input is incorporated into regulatory policy setting and decision-making (Rowe and Frewer, 2005). *Public consultation* sits between the two, offering greater opportunities for constructive conversations than public communication, but not going as far as true participation.

Meaningful public participation clearly requires more than public communication and consultation. Beyond this, however, there is not a great deal of guidance about what best practice public participation might actually entail. While there is growing support for the more active models of public participation described by Rowe and Frewer (2005), these entail associated trade-offs in terms of viability of implementation. Deliberative democracy scholars have developed models that require deep engagement with members of the public, for example through deliberative "minipublics" (Fung, 2006). For deliberative democracy scholars, then, conventional public meetings are not adequate forms of public participation (Fung, 2015). While the various forms of citizen deliberation may be feasible in the deep and broad context of regulatory policy setting, it is

difficult to see how this form of deliberative engagement could be incorporated into more routine regulatory decision-making. To require deliberative engagement for every decision about whether to approve a new drug, for example, would presumably slow the decision-making process to such an extent that it would compromise patient welfare. How, then, might public participation operate in the context of regulatory approvals for new drugs in a manner that is timely but remains legitimate, as compared with tokenistic?

Some lessons in this regard may be drawn from regulatory decision-making in the environmental and land use contexts, for which public participation has been recognised as an essential component of regulatory decision-making. In water management, for example, its crucial role is recognised in various international instruments (Mostert, 2003, 179). It has gained similar traction in the context of planning law. Over the years, however, it appears to have lost its legitimacy. Robert Stokes describes it as having become somewhat of a "sacred cow," a matter of form not substance (Stokes, 2012). Erik Mostert similarly expresses concern that public participation has become nothing more than a "bureaucratic exercise" (Mostert, 2003, 194). There is a risk that if public participation becomes a simple box ticking exercise, rather than fostering public trust, greater levels of public mistrust could result (Innes and Booher, 2004). Public trust will only result if public participation is authentic.

The public meeting laws that are a prominent feature of government decision-making in the US illustrate this point (Piotrowski and Borry, 2010; Roeder, 2013). The Federal Advisory Committee Act 1972 (FACA) and the Government in the Sunshine Act 1976 collectively require openness of meetings and minutes of meetings of federal agencies and advisory committees. As a consequence, meetings of regulatory authorities such as the Food and Drugs Administration (FDA) are required to be held in public. However, authors such as Rebecca Long and Thomas Beierle comment that, together with other factors, the actuality is that these openness requirements "may chill participation by raising barriers to members of the public who might otherwise participate," for example, through less formal consultation mechanisms (Long and Beierle, 1999, 11). As such, although open public meetings might be well intentioned as a strategy for increasing public participation, there is some uncertainty about their true value and associated costs.

Ultimately, the question of what constitutes legitimacy in public participation will depend on the context and goals of the participatory exercises. Relevant considerations include the *quality* of the exchanges; the *inclusiveness* of engagement with members of the public; and the *effectiveness* of that engagement, being the degree to which engagement meaningfully influences the regulatory position that is eventually adopted (Quick and Bryson, 2016). It thus becomes clear that the normative rationale for public participation must be properly articulated at the outset.

Why Transparency?

Transparency can be thought of as one aspect of the process of public participation. Public participation will be a meaningless exercise if it is not underpinned by a commitment to transparency and accountability. However, transparency also extends beyond this. Transparency in the context of governmental decision-making has been described as "that which "shines through" or "shows through" from an agency to its viewers," translating as "the ability to view the agency's inside, to see across the border separating the public from the agency's internal decisions" (Carpenter, 2017). For those who seek to gain access to governmental information, transparency will depend on such factors as the availability of information, the information's accessibility, and the manner in which the information may be used to support decision-making processes (Turilli and Floridi, 2009).

Transparency has been demarcated into two kinds of openness: *transparency in process* and *transparency in rationale* (Mansbridge, 2009; Licht et al., 2014). Under this delineation, transparency in rationale refers to "information on the substance of the decision and of the facts and reasons on which it was based." In contrast, transparency in process refers to "information on actions such as deliberations, negotiations, and votes that took place among and between the decision makers during the decision-making process and were thus directly fed into the decision" (Licht et al., 2014, 113).

Transparency has been promoted as bringing a number of benefits for governmental decision-making. One such benefit is *normative* in nature: that is, the general belief that public institutions should be open and transparent, rather than closed and secretive (Licht et al., 2014). As articulated by former Commissioner of the US Food and Drug Administration (FDA) Donald Kennedy, "government decisions, particularly regulatory decisions, should be based on publicly available information" because "people affected by government decisions have a right to know the basis on which they are made" (Sharfstein et al., 2017).

Other benefits are *instrumental* in nature: that is, they can improve the process of governing. For one, transparency can promote accountability and prevent arbitrary decision-making based on the availability of a clear set of rules against which members of the public can assess government decisions (Hood, 2006). In addition, transparent government processes—and the facts and reasons considered as a part of those processes—can improve the legitimacy of governmental decision-making by helping members of the public understand the reasons for a decision and any countervailing arguments (Licht et al., 2014). This provides a basis upon which members of the public can judge, and make comment on, the fairness of those procedures, potentially improving the decision-making process further (Licht et al., 2014). Transparency in process can assuage any concerns that governmental decisions might reflect a narrow special interest—for example, of a drug manufacturer—rather than a broader public interest (Carpenter, 2017).

A further instrumental benefit of transparency when it comes to drug regulatory agencies stems from the link between these agencies and medical innovation. Matthew Herder provides the example of a manufacturer considering whether to explore the use of a drug for an expanded indication. That manufacturer would clearly benefit from knowing that a drug regulator had

already considered the use of that drug for the expanded indication, and had advised against it (Herder, 2014b).

However, transparency also can require certain trade-offs when it comes to governmental decision-making, including potentially negative repercussions for governmental effectiveness, trust, and accountability. For drug regulatory agencies, measures to increase transparency also must take into account the legitimate protections that medical product manufacturers may seek for proprietary information (Califf, 2017).

In terms of effectiveness, transparency has some notable benefits (e.g., limiting corruption) but "excessive" transparency or the "wrong kind" of transparency might disrupt organisational functioning. As Jane Mansbridge has noted, some negotiations are best conducted behind closed doors, without concerns about how each word said might play out in public (Mansbridge, 2009). This points in favour of transparency *in rationale* (the facts and reasons on which decisions are based) rather than transparency *in process* (e.g., making all Committee meetings and transcripts public).

Similarly, many posit a positive relationship between transparency, trust and perceptions of decision-making legitimacy (For example, Carpenter, 2017; Licht et al., 2014). However, negative effects also can result, depending on the information that is disclosed, the way that information is shared, and the availability of avenues to independently assess the veracity of information disclosed. In her 2002 Reith lecture, philosopher Onora O'Neill articulated the limits of simply making information available as a means of promoting trust. Instead of focusing on destroying secrecy, O'Neill stressed the need to "limit the deception and deliberate misinformation that undermine relations of trust." Although some strategies for increasing transparency may reduce deception, others may "produce a flood of unsorted information and misinformation that provides little but confusion" without an equal capacity for the information to be sorted and assessed by institutions and individuals who themselves are trusted. In sum, rather than focus on transparency, O'Neill pushes us to consider making ways to actively check one another's claims (O'Neill, 2002).

O'Neill's reservations about the role of transparency in promoting trust have been echoed by others, who have stressed the need for the disclosure of information to be associated with an explanation about how the information has been produced. This includes how the information has been collected, correlated, and interpreted (Turilli and Floridi, 2009), as well as credible mechanisms for holding agencies accountable for decisions made on the basis of the information (Licht et al., 2014).

The downsides of transparency articulated by O'Neill and others highlight the importance of accepting disclosure as only one part of the transparency puzzle. To achieve true normative and instrumental benefits, transparency must be linked to broader changes in decision-making processes. Matthew Herder suggests two such pathways. First, requirements for reasons for decisions should prompt regulatory agencies to more carefully weigh a course of action's pros and cons before coming to a decision. In this way, transparency in rationale should act as a form of internal quality improvement for agencies (Herder, 2014b). Transparency in rationale could further support the operation of drug regulatory agencies as "ideal social arbiters." Annette Rid and David Wendler coined this term to address situations in which an agency lacks concrete guidance on how to make a decision, particularly as regards the risks and benefits of research (Rid and Wendler, 2011). Requirements for ideal social arbiters include: careful consideration of risks and potential benefits for all affected parties; fair consideration to everyone's claims; and the treatment of like cases alike (Rid and Wendler, 2011). Each of these criteria can benefit from transparency within an agency.

Secondly, transparency of regulatory reasons as well as the information amassed to support those reasons allows independent scrutiny by "critically engaged research communities" (Herder, 2014b). Independent assessment of "the full complexity, contingency, and contested nature of regulatory decision-making" can promote regulatory legitimacy (Herder, 2014b), leading to an avenue of active checks and balances consistent with Onora O'Neill's articulation of the pathway from transparency to trust (O'Neill, 2002).

Why Accountability?

Accountability is a conditional value where an actor is required to provide an explanation and justification for their behaviour. Accountability may also require the actor to provide forms of response or redress for breaching norms of conduct. In the context of health regulation, "public accountability" means that the justification must be made generally, or to specific publics, usually in ways that are transparent and involve the participation of community members. The functional value of accountability lies in its capacity to raise the consciousness of actors, encouraging them to reflect on whether their behaviours correspond with the norms under which they operate. Whatever its formulation, "accountability in one or another forms is increasingly seen as an independent criterion for evaluating scientific research and its technological applications, supplementing more traditional concerns with safety, efficacy, and economic efficiency" (Jasanoff, 2012, 169). Accountability has two main dimensions:

1) a *relational dimension* where questions arise as to *which* of us should be accountable and to *whom* are we accountable? and
2) a *procedural dimension* that examines question of for *what* we are accountable (for eg what type of normative breach? what types of harms?) and *how* are we to be made accountable? (for eg, in what fora will the person have to give their account and what powers does that fora have to order restitution or reparations for poor behaviour?)

One cannot speak of holding someone to account unless there is a set of norms which can be used to judge the actor's behaviour. The concept of accountability therefore assumes that there are a set of agreed norms of conduct against which the particular actor's behaviour may be measured. This also requires that there must be a community or public in which the norms are generated and held. For example, in claims of scientific misconduct, a scientist will have to justify their work to other members of the scientific community. That community holds tightly to norms of conduct, data integrity and repeatable findings and the scientist must be prepared to provide a proper account of how the results

in a publication were achieved. In the absence of such an account, they face sanctions like retraction of an article or loss of research income.

Similarly, in a case where a doctor is facing allegations of misconduct for providing unconventional treatments, the doctor will be held accountable for that behaviour by comparing the treatments with reasonable professional practices from the same field. The doctor must justify their departure from those standard practices before a medical board or tribunal and failure to do so may result in their practice being restricted or prevention from practising altogether. It is also worth noting that the choice of public to which a person is held to account is a political and social one, and the interplay of these forces may deem an actor to be accountable to several publics at the same time, or to none.

Accountability is therefore susceptible to failure in all its dimensions. From the relational dimension, it may fail when there is no authority to whom actors must provide an account, for example no regulator, or no license authority. In the procedural aspect, failure may arise from a lack of a forum in which to require actors to provide an account, or from a lack of agreed standards or norms within a public. And failure may also occur in the battle between publics as to which of them can set standards of behaviours and hold particular actors to account (for example, if a doctor seriously injures a patient, when should the doctor be held criminally responsible for injuring a patient, responsible in tort law and/or professionally disciplined?).

In the drug regulatory context, this raises questions as to whom a regulator is responsible when issuing (or failing to issue) an approval, the standards on which this responsibility should be based, and how such obligations link back to expectations of transparency and public participation.

LESSONS FROM CURRENT REGULATORY PRACTICES

Lessons From Product Approval Processes Generally

The products of genome editing designed for use in humans will require approval by national regulatory agencies before they can be made available clinically. These agencies include the Food and Drug Administration (FDA) in the US, the European Medicines Agency (EMA) and the Australian Therapeutic Goods Administration (TGA). Cognisant of calls on governmental agencies to adopt "good governance" principles of transparency, accountability and public participation, each of these agencies has committed to disclosure of their regulatory decisions at various stages of the process of market authorisation (Papathanasiou et al., 2016; Califf, 2017; Sharfstein et al., 2017). Specific mechanisms for achieving these ends range from simply requiring registration of clinical trials and summary results, to publication of reasoning behind regulatory decision-making (Herder, 2014b).

Notably, the EMA and TGA both have a stated commitment to disclosure of information leading to rejection of applications as well as approvals (Papathanasiou et al., 2016). Since 1995, European Public Assessment Reports (EPARs) published by the EMA have provided public access to a range of information, including most relevantly, assessment and product information reports for all medicines, whether approved or refused (European Medicines Agency, 2018b). The Australian TGA has implemented a system modelled on the EU system, and produces similar information in the form of Australian Public Assessment Reports (AusPARs) (Australian Government Department of Health Therapeutic Goods Administration, 2021a). AusPARs have been published since 2009 for prescription medicine applications (including biologicals). These systems resulted from commitments on the part of the EMA and TGA to increase transparency, although given the confidential nature of some information provided during clinical trials, commercially sensitive information is redacted (Papathanasiou et al., 2016). AusPARs are produced by the TGA for "major submissions" relating to prescription medicine applications for new chemical and biological entities. They are described by the TGA as "...an important part of the transparency of the TGA's decision-making processes" (Australian Government Department of Health Therapeutic Goods Administration, 2021b).

In the US, the FDA has been less proactive in sharing data relating to clinical trial decision-making and outcomes. While there are clear requirements for industry submission of data relating to clinical trial protocols and results (DeVito et al., 2020), the FDA does not currently disclose its own analyses pertaining to regulatory assessments. Currently, FDA analyses are only released on an individual basis pursuant to freedom of information requests. Although "applicable" clinical trials are required to be registered on a publicly available registry, such as clinicaltrials.gov, information published by the FDA about clinical trials and approvals is limited to study design, administrative information and summary trial results. Further information is disclosed in the case of some medicines where the FDA considers it necessary to establish and consult advisory committees. In this instance, the meetings of these advisory committees are public and the minutes published (Sharfstein et al., 2017). There have been calls for greater sharing by sponsors and investigators of clinical trials data (Committee on Strategies for Responsible Sharing of Clinical Trial Data, 2015), but also ongoing calls for increased disclosure of information held by the FDA, including clinical study reports, clinical trial data, and FDA analyses in relation to both approved and rejected applications (Sharfstein et al., 2017). Restrictions on access to information are justified by the FDA on the basis of confidentiality. Yet although the non-disclosure of confidential, commercial data is mandated by Congress, the FDA has considerable flexibility to interpret what falls within the confines of non-disclosable, confidential data (Kapczynski and Kim, 2017).

Notwithstanding calls for increased or comprehensive disclosure by the FDA of clinical trial data and regulatory assessments, which would bring it into line with the EU and Australian systems, there is a strong argument that increased transparency alone is insufficient. While it undoubtedly reflects transparency in the *rationale for* individual decisions, it fails to exhibit transparency in the *process of* decision-making. It also neglects to incorporate public participation in grounding

decisions to approve or reject applications. Publishing clinical trial data alone does not equate to effective public participation, because it permits no feedback from trial participants or other relevant parties. In accountability terms, there are issues with the procedural dimension of applicable standards and with the question of whom decision-makers should have to account to.

In sum, there is presently very little meaningful public involvement evident in approval decisions. Public participation though consultation processes is frequently utilised in setting the boundaries of regulatory frameworks. But public participation in specific regulatory decision-making when it comes to marketing authorisation for new therapeutic products is lacking. Given the normative nature of decisions surrounding the approval of new therapeutic products, particularly those involving new technologies such as genome editing, some context for decisions beyond scientific reasoning would promote more meaningful decision-making.

Lessons From Gene Therapy Market Authorisations

Beyond the public participation embedded in product approval processes more generally, it is helpful to consider the specific regulatory pathways likely to apply to products of genome editing. At present, the best comparator is the regulation of gene therapy products given that genome editing is likely to be regulated in a similar manner. This raises the question of what role the three pillars of public participation, transparency and accountability play in this context?

Although regulatory authorities have had limited opportunity to consider and approve gene therapy products,[1] there are a number of projects in the pipeline that look set to test the capacity of regulatory authorities in coming years, as the number of gene therapies in the development pipeline increases (O'sullivan et al., 2019; Horgan et al., 2020). Because gene therapies often treat rare diseases, they are not usually assessed through submission of data from large scale clinical trials. Rather, sponsors frequently rely on trials that involve small numbers of patients and the development of novel clinical endpoints (High, 2020). While traditional clinical trial pathways govern personalised medicine therapies, patients are likely to have to rely on lobbying for individual access to medicines, through pathways for compassionate use (Australian Council of Learned Academies, 2018). These pathways rely less on evidence and more on responding to desperation on the part of patients (Lewis et al., 2017). All of these distinctions have relevance for the manner in which public participation, transparency and accountability feed into approval processes.

The European Union

Under the EU regulatory scheme, biologic products are brought within the scope of the medicinal products scheme (Medicinal Products Directive 2001/83/EC and Regulation (EC) No 726/2004), by the Advanced Therapy Medicinal Products Regulation 2007 (ATMP Regulation). Products will fall within the ATMP scheme if cells or tissues have been "engineered." This requires them to have been subject to "substantial manipulation" in order to achieve particular biological, physiological or structural properties, *or* that was intended to achieve a function differing from their original function (Art 2(c) ATMP Regulation).

ATMPs may be developed in line with the traditional therapeutic development pathways. The EMA's Committee for Advanced Therapies (CAT) provides specialised scientific advice on advanced therapy applications, as well as general scientific advice (European Medicines Agency, 2018a. Aside from conventional development routes, CAT provides a certification procedure for ATMPS being developed by small and medium-sized enterprises (SMEs). This procedure certifies compliance with the standards for issuing a marketing authorisation on the basis of available "quality and non-clinical data" and is available to provide an incentive for SMEs to develop ATMPs. In some cases, products in development may also be made available to groups of patients with unmet need, under very strict conditions, through the compassionate use pathway.

There is limited evidence of EMA consideration of patient perspectives in risk-benefit analyses conducted during conventional therapeutic processes, but increasingly there have been calls to elevate patient input into decision-making by Health Technology Assessment (HTA) bodies (Coulter et al., 2008; Sarri et al., 2021), and some moves by the EMA to involve patients in decision-making (Mühlbacher et al., 2016). There is some scope for those developing *innovative* medicines to apply to follow alternative pathways for approval, some of which provide greater opportunity for early patient dialogue and consultation in relation to regulatory decisions than conventional approval pathways. For example, scientific advice may be sought in some cases where innovative technologies are being developed and it is appropriate to deviate from traditional development pathways. (Nicotera et al., 2019). Protocol assistance is the term given to advice provided by the EMA in the development of orphan medicines for rare diseases. Accelerated assessment is available for priority medicines in areas of unmet clinical need whereby support for development is provided by the EMA (European Medicines Agency, 2018c). All of these processes provide a forum for more systematically recording and incorporating the opinions and experiences of patient representatives from an early stage, and iteratively engaging with patients (among other stakeholders). They are likely to better take into account the 'trade-offs 'weighed by patients, which can differ to those taken account of by regulators (Mühlbacher et al., 2016).

The EMA has also adopted an Adaptive Pathways approach, (European Medicines Agency 2018a) described as "a prospectively planned, iterative approach to bringing medicines to market" (European Medicines Agency, 2016). The premise behind the scheme is that testing of particular therapeutic products will be directed toward carefully defined groups of patients with 'high medical need' who are likely to benefit from the treatment, rather than gathering data through conventional routes (European Medicines Agency, 2018a). The process for approval may occur in stages and involve limited

[1]As of the date of writing, 14 gene therapy products have been approved and marketed in the EU, 20 in the US, and just three in Australia.

patient populations. It may also incorporate evidence gathered through discussions between sponsors, regulators and other relevant parties, including patient representatives whose participation and input is encouraged (European Medicines Agency, 2016). To be effective, these discussions generally need to take place prior to phase II trials (Nicotera et al., 2019). A pilot project initiated in 2014 was reported to have provided a successful pathway for a number of products fitting the application criteria, which enabled contributions to be made by patient group representatives among others (European Medicines Agency, 2016).

Australia

The application of the Australian TG Act to the products of gene therapy and genome editing is complex, with legislative differentiations based on whether products are made *with* versus *from* human cells or tissues, and whether use is *in vivo* or *ex vivo*. (Nicol and Eckstein, 2019). The TGA has advised that gene therapy products are regulated as medicines under the *Therapeutic Goods Act 1989* (Cth) (TG Act) where gene therapy is performed *in vivo*. Where performed *ex vivo*, gene therapy will be regulated as a biological (Smith, 2019). Genome editing is likely to be regulated in a similar manner. Although both medicines and biologicals will require review by the TGA in order to be listed on the Australian Register of Therapeutic Goods, the process for review will be subject to some differences (e.g., the reviewing advisory committee).

The TGA's approval processes closely mirror those under the EU scheme. While traditional regulatory pathways are the norm, several special access schemes exist under the TG Act (sections 18(1), 32CA (2) and 41HA; regulation 12A of the Therapeutic Goods Regulations) which access to unapproved therapies may be sought. At the time of writing, the TGA has approved just three gene therapy products, one *in vivo* and two *ex vivo*. Kymriah was approved in December 2018, Luxturna in August 2020 and Zolgensma in February 2021. Because Kymriah is delivered *in vivo*, it was assessed through the TGA's medicines pathway. Luxturna and Zolgensma were assessed via the biologicals pathway.

In the standard product approval processes for both medicines and biologicals, there is little evidence that the TGA currently takes into account patient preferences, transparency and pillars of accountability in regulatory decision-making. TGA reviews are conducted in private, and are not open to public input (Eckstein, 2015). Expertise is made available to the TGA through relevant advisory committees (e.g., the Advisory Committee on Biologicals), however—with the exception of one consumer representative—committee members are medical researchers and clinicians (Australian Government Department of Health Therapeutic Goods Administration, 2020). With respect to transparency, AusPARs are prepared by the TGA and made available on its website for "applications where the significance to the public is considered to be high," including for submissions that have been approved, withdrawn, or rejected in the application process (Australian Government Department of Health Therapeutic Goods Administration, 2021a). AusPARs for the gene therapy products mentioned above indicate close reliance by the TGA on European and US trial results and regulatory outcomes, (Australian Government Department of Health Therapeutic Goods Administration, 2021b), which is unsurprising given the innovative nature of these therapies.

The need for public input in taking genome editing and other breakthrough technologies into the clinic has been recognised, but the challenges in doing so and in achieving meaningful outcomes at critical stages of the regulatory process have been acknowledged (Australian Council of Learned Academies, 2018). Few public engagement mechanisms have been tested in Australia to date (Australian Council of Learned Academies, 2018).

Special access scheme pathways provide another potential opportunity for public participation. Category A applies to terminally ill patients, who may be supplied with unapproved drugs by their medical provider based on notification only to the TGA where death is likely to be imminent. Category C allows medical providers to apply to the TGA to supply specific unauthorised goods to patients or groups of patients on an ongoing basis where products have an established history of use, making it inapplicable at present to products of gene therapy or genome editing (Australian Government Department of Health Therapeutic Goods Administration).

In addition to clinical trials, perhaps the most relevant category is Category B, which may be relied upon by patients with non-serious or life-threatening illnesses and an unmet clinical need. These patients may by supplied with unapproved goods, subject to TGA approval. Because Category B approvals require a higher threshold than Category A approvals, it is difficult to predict whether it would be reached for gene therapy or genome editing products, even where patients are prepared to accept the risks of therapy. The requisite tests of "seriousness" and "unmet need" are likely to present interpretational difficulties (Von Tigerstrom, 2015).

The United States

US regulation of the products of gene therapy is undertaken pursuant to the Code of Federal Regulations (Title 21CFR), enacted under the Federal *Food, Drug and Cosmetic Act* (FD&C Act) The agency overseeing the regulation of biological products is the Center for Biological Evaluation and Research (CBER). Because gene therapy involves "more than minimal manipulation" of cells, tissues and cellular and tissue-based products (HCT/Ps), it is regulated under the biologics regulatory system comprising the *Public Health Service Act,* § 351 and the Human Cells, Tissues and Cellular and Tissue-based Products Regulation (21 CFR Part 127). For cells or non-structural tissues, "minimal manipulation" means processing that does not alter biological characteristics. "Minimal manipulation" in respect of structural tissue means processing that does not alter the original characteristics relating to reconstruction, repair or replacement.

In addition to clinical review by the FDA, gene therapies have previously been subject to review by the NIH Recombinant DNA Advisory Committee (RAC). This dual oversight system was concluded in 2018 when primary oversight was handed to the FDA, removing duplicative effort and reflecting the fact that gene

therapy is now viewed as having no greater risk than other fields (Collins and Gottlieb, 2018). The RAC will function as an advisory board on emerging biotechnologies going forward (Collins and Gottlieb, 2018). The FDA has also published a number of guidance documents for developers of gene therapy products (Center for Biologics Evaluation and Research, 2021.

A number of accelerated approval procedures are available for gene therapy products under the US scheme. Section 506(g) of the FD&C Act provides a procedure to designate a regenerative medicine therapy as a "regenerative advanced therapy" (RMAT) if it meets certain criteria (Food and Drug Administration, 2019). This provides a sponsor with the capacity to undertake accelerated procedures that are available, including fast track designation, breakthrough therapy designation, RMAT designation, accelerated approval and priority review designation. Specifically, the treatment must be to treat a serious disease or condition or address an unmet clinical need. Depending on the designation given, data demonstrating efficacy may be derived from surrogate or other clinically significant endpoints permitting consideration of preliminary clinical evidence (Food and Drug Administration, 2019). Novel approaches to clinical data collection are encouraged, as is the obtaining of input from patient communities. This direction is not new—indeed it is in line with general FDA guidance focused on the incorporation of patient input into risk-benefit analysis (Food and Drug Administration, 2020). The more general FDA guidance provides recommendations as to how patient preferences and experiences may effectively inform risk-benefit assessments in conducting clinical studies. A further necessary step is building capacity amongst researchers to effectively capture qualitative data on patient preferences, and amongst regulators to successfully evaluate this study data (Johnson and Zhou, 2016).

Further initiatives to increase the weight of patient preferences in decision-making include a program by the FDA which ran a series of workshops between 2013 and 2018 focused around particular diseases, in which input of patient advocates was a key component (Center for Drug Evaluation and Research, 2021b). The input of many thousands of patients was captured in a series of 25 patient input reports. The initiative was a core component of the Center for Drug Evaluation and Research's (CDER) Patient-Focused Drug Development Initiative, a "systematic approach to help ensure that patients" experiences, perspectives, needs, and priorities are captured and meaningfully incorporated into drug development and evaluation' (Center for Drug Evaluation and Research, 2021a).

Growing patient participation in decisions relating to drug development appears to be improving transparency and accountability by drug developers (Wicks et al., 2011; Lowe et al., 2016). Increasingly there are moves by the FDA to incorporate patient experience into risk-benefit analyses in relation to particular applications before the FDA. However, this expansion in normative consideration of patient perspectives has not consistently resulted in incorporation of patient views at the regulatory evaluation stage, particularly for therapeutic products progressing through conventional approval pathways. There is real scope with products aimed at rare conditions (and in which clinical evidence is often lacking), to address this imbalance.

A patient involvement pilot for orphan drugs in Canada provides a useful starting point for investigating the potential methods through which patient involvement in the medicines evaluation process (Klein et al., 2016). Data detailing patients' views was generated through questionnaires designed to elicit qualitative information on patients' quality of life, experience with existing therapies, unmet medical needs, and level of risk patients were prepared to tolerate. This information is sometimes gathered through the clinical trials process, but that process is inevitably concentrated on gathering of quantitative evidence. Certainly, there is scope for increased consideration of patient preferences and experiences.

Lessons for Genome Editing

Taking patient views and experience into account is by no means an easy exercise. Genome editing is a case in point: there is no clear methodology in weighing the risks and benefits of passing on heritable traits that may ensue from genome editing. Being cognisant of the scientific evidence as to risks involved remains paramount and must be communicated to patients in order to ground patient opinion in objective fact. Dialogue must be two-way, direct, and incorporate the views of broad societal interests rather than select groups (Sturgis, 2014).

Several decisions of the FDA illustrate the point that patient participation must be approached with caution, and that it must be tempered with scientific evidence in drawing the boundaries of public participation and ensuring the safety of all approved therapies and medicines. Approval through the accelerated approval process of the Duchene Muscular Dystrophy drug Eteplirsen went against the recommendations of FDA staff and an advisory committee, and proceeded on the basis of a twelve-person trial, and testimony by patients, families and advocates (Schwartz, 2017). While the approval was positively received by patients, FDA staff expressed concern that scientific evidence (or rather the fact that scientific evidence was lacking) was not prioritised (Railroading at the FDA, 2016).

In 2021, the FDA granted marketing approval to Biogen for its Alzheimer's drug Aduhelm (generic name aducanumab), using the accelerated approval pathway and surrogate endpoints: namely a reduction in amyloid-beta plaque. (Mullard, 2021). Aduhelm marks the first drug approved that targets the underlying cause of Alzheimer's rather than just the symptoms. Further clinical trials will now be required to gain final approval, but in the meantime, a select group of patients will be prescribed the drug at a cost of US$56,000 per year (Armstrong, 2021). This is despite the available clinical trial data revealing some not-negligible side effects in a significant number of patients and ongoing questions about the drug's efficacy (Mullard, 2021). At least one factor in the drug's approval appears to have been lobbying by the Alzheimer's Association, with the association's CEO stating that "Clearly, this is not a cure, and it is a marginal difference for people, but a marginal difference can make a real difference for people who have only the devastation of Alzheimer's to look to" (Feuerstein et al., 2021).

As with Eteplirsen, the advisory committee considering the drug recommended against approval. It was unanimous in its rejection, and the FDA's decision has resulted in the resignation of a committee member (Joseph, 2021). In this respect it runs counter to previous FDA practice, whereby approvals and advisory committee recommendations strongly align (Zhang et al., 2019). The Aduhelm decision, in particular, has divided the research community, with many claiming it has the potential to stymie research, erode public trust in regulatory agencies, and cause real harm to patients using the drug for no clear benefit (Mullard, 2021) It raises the question as to whether the pendulum has swung too far in favour of incorporating normative views of risks and benefits—including benefits based on untested surrogate endpoints—at the expense of scientific evidence.

FUTURE STRATEGIES TO BETTER INCORPORATE PUBLIC PARTICIPATION, TRANSPARENCY AND ACCOUNTABILITY IN MARKET AUTHORISATION OF GENOME EDITING PRODUCTS

Although the preceding discussion highlights some attempts to better facilitate public participation, transparency and accountability in public health regulatory decision-making, such steps have been piecemeal and, in some cases, controversial. Disclosure has formed a key component of the transparency arsenal of many regulatory agencies. The adequacy of such disclosures in satisfying the commitment to transparency has been subject to criticism (Kapczynski and Kim, 2017; Sharfstein et al., 2017) and appears to have limitations in practical uptake. Going beyond disclosure of information, there are increasing calls for these agencies to be more democratic in their decision-making generally, and to move away from an exclusive focus on the technical benefit-risk calculation (Jasanoff et al., 2015), towards "a more participatory, public model of drug regulation" (Herder, 2014a, S131). However, these must be balanced with ongoing respect for scientific evidence. Sheila Jasanoff's pioneering concept of "technologies of humility" provides one such opportunity.

It is useful here to reflect upon Jasanoff's dual concepts of regulatory *technologies of hubris* and *technologies of humility* (Jasanoff, 2003, 2012). Jasanoff defines technologies (or regulatory methods) of hubris by reference to traditional regulatory cultures of the 20th century that focussed on predictive methods and risk assessments and that targeted the facilitation of "management and control, even in areas of high uncertainty" (Jasanoff, 2012, 178). The focus of these regulatory techniques is to allow the public to feel confident in decision-making through reliance on scientific expertise, but the cost of using such regulatory techniques is that they downplay the limitations of expertise, and stifle public participation and policy review. Given their narrow focus on scientific expertise, technologies of hubris are also ill-equipped to deal with challenges that arise from outside of their cultural frames.

As a response, Jasanoff has proposed the adoption of regulatory *technologies of humility* to complement technologies of hubris. This requires positively including the consequences of uncertainty in the policy frame; making the normative and cultural assumptions of scientific expertise explicit, and acknowledging the plurality of values that exists concerning emerging health innovations. She argues that the development of technologies of humility should have a framework that incorporates four focal points, these being "*framing, vulnerability, distribution, and learning*" which underscore the normative questions "what is the purpose; who will be hurt; who benefits; and how can we know?" (Jasanoff, 2003, 240):

1) *Framing*: Frames are "interpretive schemata and ordering devices that are needed by policy-makers to structure the reality of a policy issue" (Dekker, 2017, 129). Frames set values and rank them in order of importance. They create a structure around what is problematic and they also provide suggested solutions. But frames can also exclude values, factors and experience which may later prove to invaluable. Techniques should therefore be adopted to make sure that frames are tested and revisited and revised in systematic and iterative ways.
2) *Vulnerability*: Traditional risk-based assessments lack an understanding of the social determinates of risk but even recent attempts to include socio-economic determinates operate at a population level, with no methods for listening to or understanding individual differences. Jasanoff argues that individuals need more meaningful ways to participate. She states that "through participation in the analysis of their vulnerability, ordinary citizens may regain their status as active subjects, rather than remain undifferentiated objects in yet another expert discourse." (Jasanoff, 2012, 180).
3) *Distribution*: It would be rare for ethical issues of distribution to be included in policies for the approval of health innovations. Policies should include consideration for how new technologies will be distributed including the kinds of disparities and realignments that may occur when new technology is introduced into populations.
4) *Learning*: Jasanoff argues that while policies often include lessons for learning from errors, mistakes and failures, there is a tendency to assume there is one set of factors which explain failure, and they should rather be designed to take into account "Ways to design avenues through which societies can collectively reflect on the ambiguity of their experiences, and to assess the strengths and weaknesses of alternative explanations." (Jasanoff, 2012, 181).

What might models that bring technologies of humility into future discourse and regulatory action in the genome editing sphere encapsulate? In **Table 1**, we provide some preliminary thoughts as to how considerations that might better incorporate technologies of humility could be captured to support the three pillars of public participation, transparency and accountability. While further work is needed to comprehensively assess these proposed mechanisms, we can use the lessons learnt from recent

TABLE 1 | Options for incorporating technologies of humility into marketing authorisations for genome editing products.

	Public participation	Transparency	Accountability
Framing	Build policy frames around participatory modelling which includes various publics (scientists, consumer groups, communities who may have particular genetic conditions)	Make the policy frames for genome editing, and decisions based on these policy frames, explicit and reviewable on a regular basis	Clearly articulate the core normative values of the policy, why those values were chosen, and which publics are offered opportunities to provide input on specific applications
Vulnerability	Develop and implement systems for ensuring that vulnerable communities can speak to issues affecting them	Publicly identify vulnerabilities and types of harms created by genome editing generally, and specific to particular genome editing applications	Provide a clear choice of forum for breaches of policy. Ensure a compensation system for harm
Distribution	Develop and implement systems for public deliberation on how access will be provided to genome editing, who will pay for it, and how/with whom any ongoing clinical trials will be conducted post-approval	Clearly articulate the economic and social values that were at play in distribution decisions	Provide social welfare support systems for care of those harmed by genome editing
Learning	Ensure review and assessment of systems of participation models	Ensure review and assessment of knowledge provision and transfer. Ensure review and assessment of regulatory approval/rejection decisions and decision-making processes	Ensure review and assessment of failures, harm incidents

regulatory setbacks to inform normative regulatory decision-making in genome editing.

Jasanoff herself recognised the modesty of the focal points identified as a "starting point" for engaging in deeper social discourse on the ethical and political implications of emerging technologies (Jasanoff, 2003). The relatively superficial evaluation of these focal points undertaken here highlights the range of considerations that are often overlooked in a traditional, hubristic model of regulation. In the interests of encouraging public trust and engagement, and injecting social considerations pertaining to risk analysis into governance, the development of models for regulating genome editing should be approached systematically, ethically, inclusively and with caution.

CONCLUSION

In this article, we have shown that both policy makers and regulators charged with responsibility for market approvals for new healthcare products support adoption of public participation, transparency and accountability in their policy-making and decision-making. However, the rhetorical force of these statements is difficult to translate into concrete actions. The path to true adoption of public participation, transparency and accountability in regulatory policy-making and decision-making for genome editing products is strewn with boulders. On the one hand, slavish adoption of these principles could reduce the weight given to scientific evidence. On the other hand, formalisation of these principles could result in them being applied in a tokenistic fashion. New models are urgently needed, particularly given the speed with which genome editing is being adopted in the laboratory and promising new genome editing product leads are emerging. We have proposed that one such model, Jasanoff's technology of humility, is worthy of consideration. There will doubtless be others. In this article, our aim to contribute to the start of a deeper conversation about these vitally important issues.

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

All authors have contributed equally to the conceptualisation of this article. JN wrote the first draft of the substantive analysis of regulatory approvals and gene therapy market approvals. All authors contributed equally to first drafts of the rest of the article. All authors contributed equally to further drafts of the article, including the final submitted version.

FUNDING

This research was supported by a grant from the Australian Research Council, DP180101262.

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frontiers in Political Science

ORIGINAL RESEARCH
published: 25 October 2021
doi: 10.3389/fpos.2021.731496

The Geographies and Politics of Gene Editing: Framing Debates Across Seven Countries

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This article traces the contours and dynamics of the debates about the politics of gene editing. It does so by providing both a quantitative and qualitative analysis of the publications on the topic. We present a scientometric analysis of scientific publications; we discuss the geographies of gene editing by analysing the scales and spatial terms mobilised; and we undertake a lexicometric analysis of how debates are framed and the public is positioned. Our scientometric analysis of scientific articles shows that the governance and regulation of gene editing is discussed across an increasing range of disciplines and countries over the years. Along with this internationalisation and "transdisciplinarisation," we see a qualitative shift in the "grounding" of the debate: while initially, authors tend to reflect about gene editing, in more recent years, there are increasing calls to act upon current knowledge. Across the countries we studied (the United States, the United Kingdom, Germany, China, Australia, Japan, and Canada) our lexicometric analysis shows only a few differences in terms of how gene editing is discussed. While the general framing of the debate is widely shared, the differences that we observe concern for instance the applications or benefits of gene editing and the ways in which the importance of involving the public is worded. We hold that bringing together multiple methods allows a rich and multifaceted discussion of the politics of gene editing, and that this opens up fertile dialogues between geography, sociology and political science.

Keywords: gene editing, governance, quantitative methods, scientometrics, lexical analysis, geography

OPEN ACCESS

Edited by:
Michael Morrison,
University of Oxford, United Kingdom

Reviewed by:
Courtney Addison,
Victoria University of Wellington, New Zealand
Brigitte Nerlich,
University of Nottingham, United Kingdom

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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: *01 October 2021*
Published: *25 October 2021*

Citation:
Meyer M and Vergnaud F (2021) The Geographies and Politics of Gene Editing: Framing Debates Across Seven Countries. Front. Polit. Sci. 3:731496. doi: 10.3389/fpos.2021.731496

INTRODUCTION

Gene editing technologies, in particular CRISPR/Cas9, have been discussed in a significant number of articles, reports, position statements, and comments. While CRISPR sequences were first described in 1987, it is only since the 2000s that their ability to "edit" genes has been recognized and studied (the name CRISPR, for Clustered regularly interspaced short palindromic repeats, dates from 2002 and Cas9 is the name of an enzyme capable of cutting DNA). It must also been stressed that ideas and methods for introducing new genetic material into organisms and/or cells have become prominent since the 1970s (Morange 2017). CRISPR/Cas9 has been welcomed as a particularly precise, cheap and simple technology to modify genes, in particular in comparison to other gene editing techniques (such as those based on zinc finger nucleases or TALEN). At the same time, concerns have been raised about ethics, legal frameworks, risks, and new forms of inequality.

Gene editing has applications in domains ranging from health (i.e., to treat HIV, sickle cell disorders, cystic fibrosis or beta thalassemia) to agriculture (i.e., the creation of hornless cows, non-browning mushrooms and more resistant or nutritional plants) and the environment (to combat

biodiversity loss and aid threatened species, control invasive species and pests). In 2015 gene editing has become highly visible beyond academic circles. Concerns about the use of gene editing to modify the human germline were sparked by an experiment on non-viable human embryos on the β-globin gene (Liang et al., 2015). In response, several groups of scientists called for a moratorium (Lanphier et al., 2015; Baltimore et al., 2015) and the technique was featured on the cover of various magazines (i.e., The Economist, Nature and Time) and in numerous press articles. The end of November 2018 marks the beginning of the most visible episode in the controversy to date. It was sparked by scientist He Jiankui, who announced *via* YouTube the birth of two babies he had genetically modified as embryos by using gene editing. The event has been widely and intensely discussed, both within and beyond the academic world. About half a year later, another scientist, Denis Rebrikov, announced in the journal *Nature* (Cyranoski 2019) his plans to produce gene-edited babies, which also led to criticisms and calls for moratoriums. Given the significance and contested nature of the technology, two international summits have been organized (in 2015 and in 2018) and the World Health Organisation established an expert panel on the governance of human gene editing in 2018. Regarding the use of gene editing in agriculture, international conferences have also been held (i.e., at the OECD in 2018) and the status and traceability of organisms modified *via* gene editing has become a hotly debated question: should they count as GMOs or not? The most visible controversy, however, concerns the use of gene editing for humans: while its use on somatic cells (which are not transmitted to descendants) is less controversial, its use on germline cells (which are transmitted) represents the crux of the debate (see Meyer 2020).

Within the social sciences, the debates around gene editing have been analysed from a variety of perspectives. Many articles have looked at the ethics and the governance of gene editing. Commentators have reflected on the first international summit on human gene editing and have called for more democracy and inclusivity, while also comparing the summit to the 1975 Asilomar conference on recombinant DNA (see for instance Jasanoff, Hurlbut and Krishanu 2015; Parthasarathy 2015; Frow 2015). Calls for an international observatory on gene editing have subsequently been made (Jasanoff and Hurlbut 2018). The governance of gene editing in the field of agriculture has also been examined, regarding differences across EU member states (Meyer and Heimstädt 2019), regarding the impasse in EU policy (with actors being either proponents or opponents of the technology) and how to get out of it (Macnaghten and Habets, 2020), and concerning NGO's views on the use of gene editing in plants (Helliwell et al., 2019).

There has also been considerable scholarship on communication and public debate. The recent special issue titled "Communicating gene editing: Agriculture, humans, and the environment" edited by Brossard and Scheufele in *Environmental Communication* (2020) provides a broad overview of public debates, opinions and engagements, and discusses various forms of communication about gene editing. Several authors have focused their analysis on the controversy sparked by He Jiankui, and studied how responsible research is demarcated from irresponsible research (Meyer 2018), what philosophical traditions can be mobilised for analysis (Yan and Mitcham 2020), and the public reactions on social media (Zhang et al., 2021). While much academic work has looked at the politics, publics, ethics and controversies around gene editing, there have also been some studies analyzing the continuities and discontinuities of gene editing in relation to existing biotechnology (Martin et al., 2020) as well as patenting (i.e., Mali 2020).

In our paper, we ask the following questions: what are the contours and dynamics of the debates about the politics of gene editing? How are these debates framed? Our paper thus aims to contribute to the growing literature on gene editing in two ways. First we offer a geographical analysis of gene editing. While many articles have discussed gene editing in a given country or territory (i.e., the EU) and many authors called for "global" and "international" governance and regulation, there are hardly any articles that address the geographical aspects of gene editing. Here, scholarship from science studies and the geography of science (Gieryn 1983, 1999; Shapin 1998; Livingstone 2005) is helpful. Inasmuch as science studies have shown that "science must take place somewhere" (Livingstone 2005: 100) and that "the global is situated" (Law 2004: 24), we hold that this also rings true for the governance and regulation of science. We hold that the governance and regulation of science is also spatially situated and arguments about their national, international or global nature need to be analysed and not taken for granted. Second, we contribute to the existing literature by undertaking an analysis that is both quantitative and qualitative. Apart from surveys about the cost of regulating gene edited crops (Lassoued et al., 2019) and about people's perceptions of gene editing (Kato-Nitta et al., 2019), the use of quantitative methods to analyse the social and political aspects of gene editing has been extremely rare. And, to our knowledge, the use of mixed methods has been non-existent to date. We thereby also respond to recent calls (Leydesdorff et al., 2020; Cambrosio et al., 2020) for a renewed dialogue between qualitative and quantitative/computational science studies, a dialogue that has begun to emerge in studies about synthetic biology or nanotechnology for instance, but been virtually non-existent regarding gene editing.

Our paper is structured as follows. In the next section we explain the methods that we used. Thereafter we present our results in four sub-sections, each responding to a specific question: what are the publication trends across countries, disciplines and time (3.1)? How are debates about gene editing framed in scientific publications and in reports - what are the main themes being discussed (3.2.)? What are the geographies of gene editing (3.3.)? How is the public positioned (3.4.)?

METHODS

We built our empirical corpus by compiling three kinds of documents: scientific publications, institutional reports and conference reports. First, in order to collect relevant scientific publications, we searched the Web of Science database with

specific key-words in the field "topic": "regulation," "governance," "politics" in combination with "gen* editing" (a search in "all fields" yields too many unrelated results, for terms like "regulation" can be present in the affiliation of an author). Our search yielded 358 results (we used version 5.35 of the Web of Science, before its update on the seventh of July 2021). For our analysis, we relied on the categorizations of the Web of Science, such as "research axes." Research axes have been created to unify the systems of classification within the Web of Science databases and are automatically attributed to journals. Even though such categories do have their limits (as any classification system has), they are commonly used in scientometric studies and they are considered as a key classification system of current scientific journals - according to Wang and Waltman (2016), the journal classification system of the Web of Science is more accurate than the one of Scopus.

Second, we collected reports on gene editing published by various institutions, such as ethics committees, advisory groups or scientific academies (our criteria for inclusion was that they need to specifically deal with gene editing and that they have to be reports, and not items such as statements or press releases). We searched for these reports through several sources (i.e., resources listed by the WHO working group on gene editing, references listed in reports and in academic papers, etc.). We then selected the reports stemming from the seven countries that we selected for our lexical analysis (see below), which left us with eight reports from four countries (being unable to find reports from China and Japan and having to exclude a report from Canada). Third, we have collected the written reports from the two most prominent conferences held so far in the field: the international summits on human gene editing held in 2015 and in 2018. While at first look, both summits resemble any other international academic conference, they are quite particular events: they were organized in response to a pressing issue, they were very publicized (in academic circles, but also in the media), they issued final statements and their audience exceeded well beyond the scientific community. So while other international conferences about gene editing have been held, the summits are key sites in which the politics of gene editing are made explicit and publicly discussed.

It is important to stress the differences between these three types of documents in terms of style, format and readership. The first ones are written by individual scientists and are published in academic journals, while the second and third ones are authored by various kinds of institutions (with various kinds of scientific, political and/or moral jurisdictions) and made available online. And while scientific publications and institutional reports present a rather coherent set of arguments or positions, the reports from the summits provide a more heterogeneous picture by summarising the discussions. This diversity does, however, allow us to embrace a particularly broad space of discussion, by looking at debates across disciplines and countries, and by embracing both the academic world and the policy world.

We read the abstracts of the 358 articles and we discarded 26 articles that did not explicitly address the regulation and governance of gene editing. We then decomposed our analysis of the 332 remaining articles into two steps. In the first step, we focused on a classical scientometric analysis. We first set aside the 21 articles from the year 2021, to be able to compare full years. We used the 311 remaining articles to statistically describe their distribution by type of publication, by discipline, and by year. In a second step, we focused on the thorny problem of assigning a unique national origin to the collected articles. For this, we exploited the "addresses" field provided by the Web of Science, which indicates the academic affiliation of the author(s) of an article. This field can indicate the academic affiliation of an author, the academic affiliation of a group of authors, or the different academic affiliations of the same author.

Attributing a country to a scientific publication by using the academic affiliation of its author(s) is a common procedure in scientometric studies. While this does not allow inferring the advancement of scientific fields in a country, it at least allows us to describe the growth dynamics of certain scientific fields in a given country (Monroy and Diaz 2018). On the other hand, a lexical analysis is a statistical method that aims to classify statements in a way that represents their broad dimensions (Lahlou 1994). In other words, using a lexical approach on a corpus of texts amounts to describing "about what" authors talk in this corpus (Fallery and Rodhain 2007).

By extension, in our study, cross-referencing the country of a scientific publication with the lexical analysis of its content (its abstract) thus makes it possible to describe how the content of this publication (the governance and regulation of gene editing) is discussed within the country of this publication (the country of affiliation of its authors). There remains the question of co-authorship: in which country does one classify a publication if co-authors have their affiliations in different countries? Comparing the country distribution by continent of the totality of the authors of our original corpus of 300 publications to the country distribution by continent of the totality of the authors of the 241 remaining publications (after removing the 59 publications with co-authors), we obtain the following results (see **Table 1**).

TABLE 1 | Comparison between country distribution by continent of the totality of the authors of our original corpus of 300 publications and country distribution by continent of the 241 remaining publications (after removing the 59 co-authored publications).

	300 publications: % of authors (*n* = 809)	241 publications: % of authors (*n* = 514)
North America	38.8	42.0
Europe	36.7	28.6
Asia	12.1	14.8
Oceania	6.7	7.4
South America	3.3	5.3
Africa	2.3	1.9

If we remove co-authored publications, we find roughly the same proportions of publications per continent, except for Europe, which tends to prove that co-authorship does not have a significant influence on our corpus of data. On the subject that interests us, the publication dynamics of the countries remain almost the same with or without co-

authorship. The table also shows that on the subject of the governance and regulation of gene editing, small scientific communities do not need their larger counterparts to publish on the subject: the 2-point difference found in South America and the 2.7-point difference in Asia even tend to demonstrate a slight movement of autonomy of these countries regarding the subject.

The case of Europe is different, since the proportion of authors decreases by 8% when we remove publications with co-authors from our corpus. We can interpret this as being due to an important integration of European countries in science. Already in the early 2000s, a scientometric study described the increase in the density of relations between scientists in European countries, driven by the success of European R&D programs (Frenken and Leydesdorff 2004). In 2008, another study concluded that the Europeanization of co-authorship of European scientists was more important than its internationalization (Mattsson et al., 2008). This movement also appears in our study, and tends to demonstrate an important intra-EU transnational partnership of European authors on the subject of the governance and regulation of gene editing. Nevertheless, in order to distinguish differences between European countries, we have, in what follows, chosen not to group European countries into a single entity.

We therefore constituted our different corpuses *via* three phases. First, in order to present an analysis of the distribution by country of the authors of the publications collected from 2013 to 2020, we subtracted those articles for which the "addresses" field was empty (an inevitable step in scientometric analyses). 11 articles were thus subtracted, leaving us with 300 articles. Second, in order to assign a single country of affiliation to our articles, we removed articles that were written by several authors from different countries: 59 articles were removed, leaving us with 241 articles. Third, we wanted to cross-reference the "country" of an article with the lexical content of its abstract. Thus, in order to constitute a corpus for a more qualitative analysis, we took as a basis the original corpus of 332 articles, which includes articles from 2021, and subtracted 12 articles without "addresses," 26 articles without abstract, and 64 articles written by several authors from different countries, leaving us with 230 articles. Of these 230 articles, 33% are from the United States, 8.3% from the United Kingdom, 5.2% from Australia, and 4.8% from each of the following countries: Canada, Japan and Germany. A total of 60.9% of the articles are thus published by authors of the aforementioned countries.

In order to restrict our analysis to a small and manageable group of countries, while keeping a sufficient number of abstracts available for our analysis, we decided to select for the lexical analysis only articles from countries that published more than 10 articles: the United States (76), the United Kingdom (19), Australia (12), Canada (11), Japan (11), and Germany (11). However, since China is an important actor regarding the governance and regulation of gene editing, we decided to also include its articles (8 articles, equaling to 3% of the total number of articles). This eventually led us to a corpus of 148 abstracts. We are aware of the limitations implied by these decisions, but we consider that the present study represents a first synthesis of its kind, laying the groundwork for more studies to come, that could analyze more systematically articles published from all over the world on the subject.

We also contend that our corpus comprises articles that cover very different fields of application (agriculture, the environment, human health). We have analyzed them together, in order to start with–and be able to provide a picture of - gene editing as a whole. We did not differentiate our corpus regarding disciplines or fields of application before our analysis, but we wanted to let these differences emerge. Further work could thus examine to what extent findings vary when the corpus is divided according to applications and/or disciplines.

In order to do our lexical analysis, we used IRaMuTeQ. IRaMuTeQ is a program for the multidimensional and statistical analysis of a corpus of text (Ratinaud, 2021). It is based on the Max Reinert classification method (Reinert, 1983; Reinert, 1986; Reinert, 1990), an analysis which is based on a hierarchical descending classification. While IRaMuTeQ offers three classification methods, we have used simple classification in this article (see **Supplementary File SA**). This statistic classification takes place on a segment of text, and makes it possible to obtain a near exhaustiveness of the sentences of the study corpus in the final classification since the terms are compared with each other within the entire text. We build here on our previous study of online discussions about do-it-yourself biology *via* IRaMuTeQ (Meyer and Vergnaud 2020).

In parallel to our scientometric and lexical analysis, we did two qualitative rounds of analysis to examine the spatial dimensions of our corpus. First, the content of the reports from the two international summits on human gene editing was analysed qualitatively. Themes dealing with geography and space were analysed - and the content of both reports have been compared. To do so, a "selective" coding of the reports was done, by defining a core variable (space/geography) without coding any other dimensions (on coding and categorization see Kelle 2010; Thornberg and Charmaz 2014). This was done manually: all the words or groups of words that refer to space were underlined, compared and analyzed and then divided into categories. Three large categories were defined: "international context," "fragmentation and variation across countries," and "national contexts." As the kinds of arguments within the first category varied importantly, they were further divided into four subcategories: "dialogue," "governance," "techno-science," and "values/ethics" (see **Table 2**). This way of coding the data allowed us to be able to identify and examine the range of arguments used. At the same time, it also allowed us to be able to see to what extent specific categories or subcategories differ between 2015 and 2018.

Second, we did a qualitative analysis of the active word forms in our corpus ("active" word forms are nouns, adjectives and adverbs and thus exclude "supplementary" word forms like pronouns, prepositions, etc.). To do so, we read through all the 2,915 active forms to search for words describing space in one way or another. We ended up with two separate lists of words. In our first list we included words about concrete aspects of geography, which divide into three categories: the international level, the national level and the European level. In our second list, we included terms that deal with space in more metaphorical and/or abstract sense (such as "line," "barrier," "space," and

TABLE 2 | Main geographical themes (in bold) - and examples of quotes - in reports of the international summits on human gene editing held in 2015 and in 2018.

	2015 summit	2018 summit
International context	**Dialogue:** summit "brought together more than 500 people from around the world" and "Experts from many parts of the world"; "global dialogue," "international community," "global discussion"	**Dialogue:** summit brought together 500 people "from around the world" and was viewed by "visitors from over 190 countries"; "international discussion"; "international forum," "need for the global scientific and medical communities to continue to work together," dialogue between "academies around the world," "international scientific community"
	Governance: "governance is becoming increasingly international," "Governance (. . .) is now crossing geographical borders (. . .) governance is no longer just local, but is becoming a network of nations working together"; Proposal of "international ban on germline gene editing for reproductive purposes can be secured through the United Nations and regional bodies can prepare internationally binding regulations"	**Governance:** "the organizing committee calls upon national academies and learned societies of science and medicine around the world to continue the practice of holding international summits to review clinical uses of genome editing, to gather diverse perspectives, to inform decisions by policymakers, to formulate recommendations and guidelines, and to promote coordination among nations and jurisdictions"
	Techno-science: "CRISPR-Cas9 is being used in laboratories around the world," "the human genome is shared among all nations,""genetic alterations (. . .) would not remain within any single community or country," "It's no longer possible to control technologies by the laws of one country"	—
	—	**values/ethics:** "global ethical code of conduct," "universal values," "global standard"
Fragmentation and variation across countries	"governance can differ among countries," "representatives from Nigeria, Germany, France, Israel, South Africa, Sweden, and India highlighted the many ways in which policies (. . .) vary among nations (. . . and) that the needs of countries vary dramatically"	"differences in local contexts, values, and opinions"
National contexts	"countries have in place provisions that act to prohibit germline gene editing," "people will go to whichever country has it," "many nations have legislative or regulatory bans on germline modification," "each nation ultimately has the authority to regulate activities under its jurisdiction"	Contexts in Japan, sub-Saharan Africa, China, France, India, Australia, Singapore, and Hong Kong discussed; "in China an extensive regulatory framework governs genome editing"; surveys in Australia and public participation in the United Kingdom and China mentioned; "a Chinese researcher," "a researcher in China," "a particular problem with the governance of human genome editing in China," "the researcher did not follow guidelines (. . .), or other international norms"

"landscape"). For the terms of our second list, we rechecked in our corpus how they were specifically used, that is, in combination to what other kinds of words–and in what *sense* - they were used.

Rather than doing two separate rounds of analysis (one quantitative, one qualitative) we moved back and forth between a quantitative and qualitative analysis (see Akrich 2019). Both were brought into dialogue in several ways: we were able to validate and extend our lexical analysis of the reports of the international summits by theorizing how the debate became more "grounded" over time; our statistical analysis yielded a list of active forms that we re-interrogated qualitatively concerning the use of terms referring to geography; and, in more general terms, we did not stop at identifying the framings of the debates about gene editing, but also the politics of these framings (by discussing issues such as democracy and the inclusion/exclusion of the public).

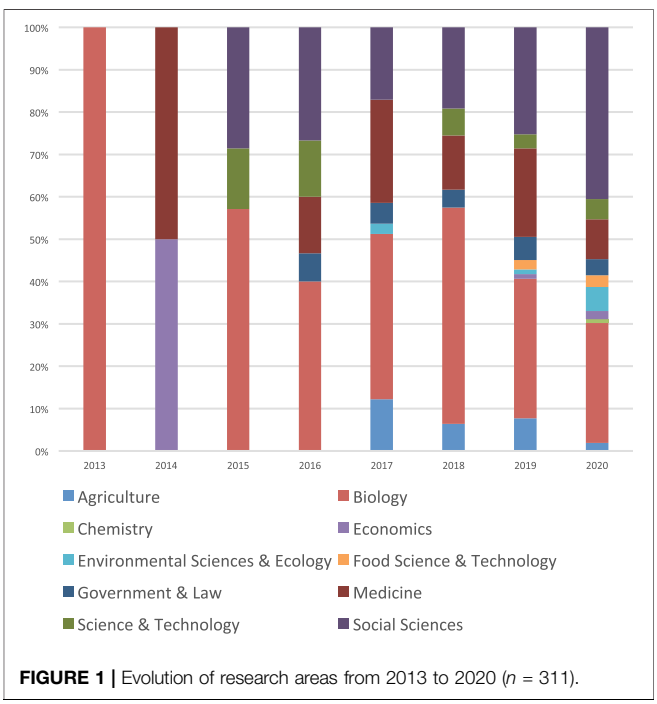

FIGURE 1 | Evolution of research areas from 2013 to 2020 (n = 311).

RESULTS

Scientometrics

Article Types and Disciplines

About 60% of the 311 publications are journal articles, 30% are either editorials or reviews, and the remaining 10% include items

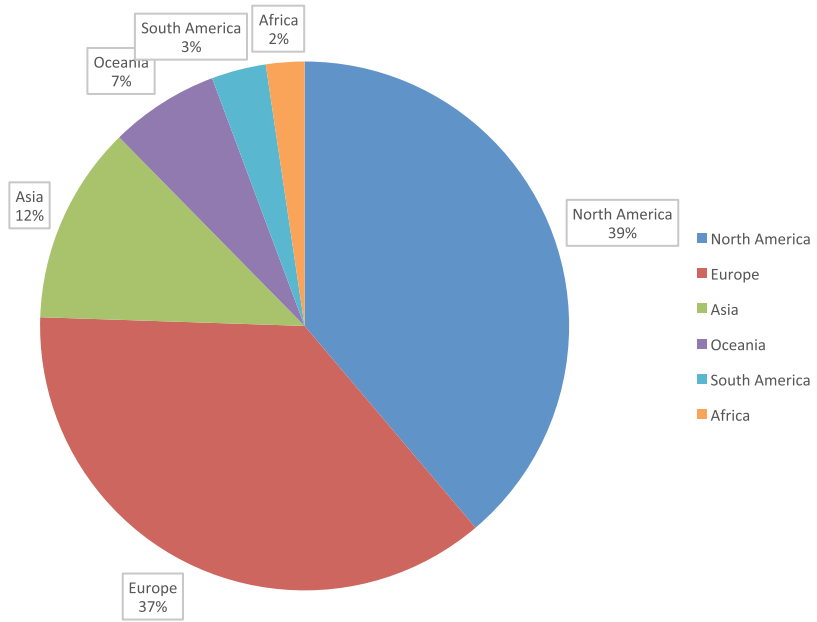

FIGURE 2 | Distribution of the academic origin of authors (n = 809).

such as book chapters, meeting abstracts, and news items. The disciplines most represented are "social sciences - other topics" (33%), "biochemistry and molecular biology" (9%), "agriculture" (7%), "biotechnology and applied microbiology" (7%), "genetics and heredity" (5%), "plant sciences" (4%). While the social sciences represent about a third of the corpus, the natural sciences represent two thirds. Within the natural sciences, genetics and molecular biology are more prominent than fields such as medicine or environmental sciences for instance.

If we regroup disciplines (such as biology, biochemistry, biotechnology, etc.), in order to see evolutions more distinctly, several trends are visible. The proportion of biology articles decreases significantly: it is divided by almost two, from 57% in 2015 to 28% in 2020 (see **Figure 1**). New fields are also emerging, such as agriculture and health care sciences in 2017 and food sciences in 2019. During the same period, the proportion of the social sciences also varies. While it has decreased between 2015 and 2017 (from 28 to 17%), there has been an increase from 2018 onwards, with 25% in 2019 and 40% in 2020. We thus see that over time, discussions about the governance and regulation of gene editing spread to a broader range of disciplines and become less dominated by biology. While the natural sciences still comprise most references, the debate becomes more multifaceted and more application-oriented over time.

Evolution Over Time

Only four articles have been published in 2013 (2) and 2014 (2). In 2015–2016, we observe a twofold increase of the number of publications, and a threefold increase between 2016 and 2017. While the years 2017 and 2018 are relatively stable in terms of output, we see another doubling in 2019, and a slight increase in 2020. There are thus two significant increases after relatively little interest in the regulation and the governance of gene editing in the period 2013–2014: the first increase (2015–2017) being arguably caused by the controversy sparked by Liang et al. (2015) and the second increase (2019–2020) being a reaction to He Jiankui's experiments.

Evolution Across Geography

About half of the authors of the publications stem from four countries: the United States, the United Kingdom, Canada and Australia. One third of the publications are written by authors from the following nine countries: Germany, China, Japan, Spain, Netherlands, Italy, France, Belgium and Sweden. If we look at publications across continents, we see that most authors are from North America (38.8%) and Europe (36.7%), a smaller number of authors stem from Asia (12.1%), and only a few articles have been published by authors from South America (3.3%) or Africa (2.3%) (see **Figure 2**). Between 2013 and 2020, we observe two trends (see **Figure 3**). There are new countries present in the corpus. Until 2016, there are principally publications from authors in Europe (France, United Kingdom, Germany, Spain, Belgium, Norway, Poland), North America and Japan. In 2017, Europe enlarges (with authors from Finland, Italy, and Sweden joining), South American authors join (Argentina, Brazil), as well as Asia (Singapore, India). In 2018, we see another extension in Europe (with Denmark, Belgium, Iceland, Lithuania, Norway and Serbia), the inclusion of African authors (Kenya, South Africa), and an extension of Asia and the Middle East (Pakistan, Oman, China). From only four contributing countries in 2015, the number rises to 21 in 2017, up to 38 countries in 2020. At the same time, there is a slight decrease regarding North America. There has thus been an

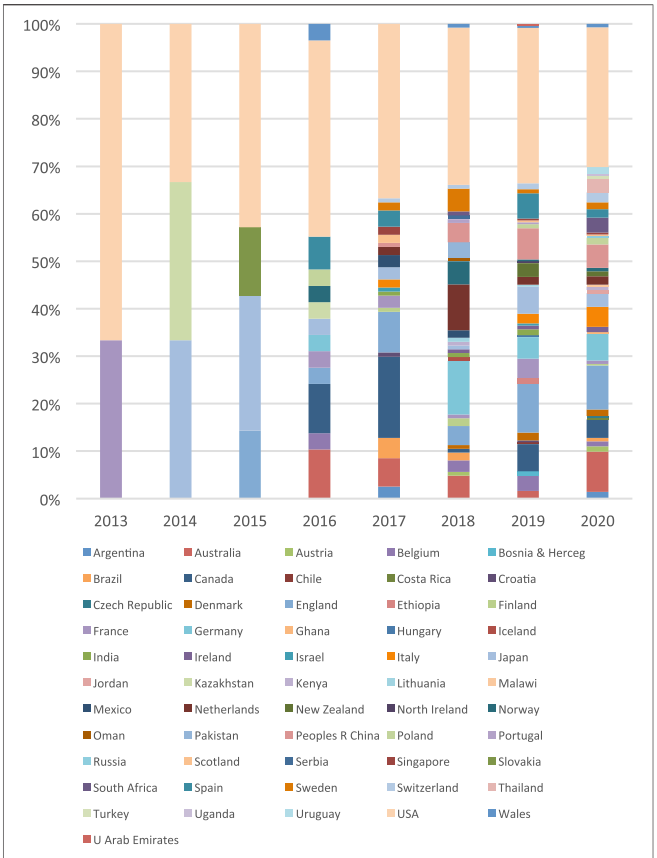

FIGURE 3 | Evolution of the institutional origin of authors from 2013 to 2020 (n = 809).

internationalisation, with North America being less prominent, and new countries joining the debate. This trend is visible in many other domains, where we see fewer publications from hegemonic countries, and new (i.e., Asian) countries increasingly present (see Kumari 2006; Glänzel et al., 2008). However, the key locus of scientific production is, still, Europe and North America. Despite the fact that there has been an internationalisation of the debates, they cannot be qualified as international.

Lexical Analysis

Summit Reports

Two international summits on human gene editing have been held to date: the International Summit on Human Gene Editing held in Washington in 2015 (National Academies of Sciences, Engineering, and Medicine, 2017) and the Second International Summit on Human Genome Editing (National Academies of Sciences, Engineering, and Medicine 2019) held in Hong Kong in 2018. We considered the reports of these two summits as a unified and coherent corpus. Our analysis of both reports provides a fairly comprehensive inventory of issues related to gene editing in the world. Three main themes are addressed: the description of the method and the targets of gene editing, governance and regulation, and the role of the public.

In 2015, the participants focused extensively on the method of gene editing and on the variety of applications: DNA, cells, blood, embryos, sperm cells, the fetus, the body. The possible benefits of its use for the treatment of certain genetic diseases or viral infections were discussed, as well as the risks of genetic modifications on future generations. Nevertheless, these future generations were discussed more succinctly, and described as being largely dependent on the policies and regulations of each country (given that governance frameworks are not uniform across countries). The organising committee wished to assess these dangers in order to comply with "ethical rules." It also hoped for the emergence of a public debate, in order to establish a "network of nations" and an international regulatory framework. In 2018, the fields of application of gene editing were discussed again, for instance in the treatment of certain genetic diseases, such as Duchenne muscular dystrophy. But it was also argued that the discussion needed to move beyond the potential targets of gene editing, be it the cell or the embryo, and look beyond cell therapies and clinical trials. For there are patients, parents, and people to be considered: the public is to be taken into account. The role of the public, and its engagement through dialogue and discussion, was thus discussed. The organizing committee also recognized the lack of transparency of certain research in progress, and pleaded for the adoption of ethical considerations in research using gene editing.

We also carried out a qualitative analysis of both reports, in order to examine more specifically the geographical arguments and terms present. In both reports, three sets of geographical arguments stand out (see **Table 2**). First, the international nature of the debate is prominent. The summit is called "global" and "international" and was attended by people from "around the world." At the same time, the governance of gene editing is qualified as "international," requiring nations to "network" and "coordinate." Second, variation and fragmentation across nations are also stressed, with the term "difference" being frequently used. Third, and relatedly, national contexts are also specified. Some nations have regulatory frameworks that allow or prohibit gene editing, and there have been surveys and engagement exercises in various countries.

Despite these similarities, there are two noteworthy differences. "Ethics," "values," "guidelines," and "norms" are featured more prominently in the report of the second summit - which has also been revealed through our lexical analysis above. While in 2015, discussions about governance and regulation were rather general and abstract, in 2018 they were discussed in relation to more tangible entities, such as written guidelines, independent assessments, scientific institutions, national regulatory authorities, prohibitions, etc. rendering the practical ramifications of governance/regulation more explicit (see Meyer 2021). We see a shift here in the "grounding" of the debate: in 2015, the scientific community came together *to reflect*, in 2018, calls were made *to act*. In 2015, the discussion was more hypothetical, with discussions about potential applications, possible benefits, and future public debates. In 2018, however, with the news that human gene editing had become a reality, we see discussions that are much more centered on decision-making with institutions and regulatory authorities being called to act.

TABLE 3 | Institutional reports analyzed.

Australian Academy of Sciences (2017). *Synthetic gene drives in Australia: Implications of emerging technologies*. Canberra: Australian Academy of Sciences.
Deutscher Ethikrat (2017). *Germline intervention in the human embryo. German Ethics Council calls for global political debate and international regulation*. Berlin: German Ethics Council.
Deutscher Ethikrat (2019). *Intervening in the Human Germline*. Berlin: German Ethics Council.
Nuffield Council on Bioethics (2016) *Genome Editing: An Ethical Review*. London: Nuffield Council on Bioethics.
Nuffield Council on Bioethics. (2018). *Genome Editing and Human Reproduction: social and ethical issues*. London: Nuffield Council on Bioethics.
National Academies of Sciences, Engineering, and Medicine (2017) *Human Genome Editing: Science, Ethics, and Governance*. Washington: National Academies Press.
National Academies of Sciences, Engineering, and Medicine (2019). *Heritable Human Genome Editing*. Washington: The National Academies Press.

The second notable difference between the two summits is the fact that China and the work of He Jiankui are discussed at length at the second meeting. He Jiankui's announcement of the birth of gene-edited babies happened at the eve of the second summit, which caused a major controversy. In the report of the summit, we read of "a Chinese researcher" and "a researcher in China," and of "a particular problem with the governance of human genome editing in China." The issue is that "the researcher did not follow guidelines (. . .) or other international norms." The summit became a site in which He Jinakui was singled out and a clear boundary was drawn between responsible science, produced in a transparent and open way, and, on the other hand, irresponsible science, produced in secret.

Institutional Reports

We then analysed the reports published by national science academies and ethical councils. We were able to analyse four countries of our corpus (Germany, Australia, the United Kingdom and the United States, see **Table 3**) - we had to exclude the report from Canada because it does not represent a "national" view (the report is not written by a national institution, but co-authored by one university and a private actor), and we were unable to find reports from China and Japan. The themes in the reports mirror the themes addressed in the two summits, but show nonetheless variations in the four countries we studied.

The description of the method of gene editing and the variety of targets and applications is taken up in unison by the reports we have analyzed. The reports generally mention the importance of taking into account the public, but there are nuances to be noted nonetheless. The US reports call for "citizens" to give their opinion, by setting up forums, debates and committees to create a dialogue with the public, to promote their engagement and participation. This mobilization should provide recommendations to be addressed to policy makers in order to create and legitimize a national policy. The UK reports tackle the subject in the form of the "societal question." Debates, dialogues, and conferences are desirable, but a certain "morality" must accompany the decisions taken in these places, which should lead to acceptable "standards" ensuring "well-being," dignity and human rights of the concerned actors (especially children). The German reports raise the question of justice. Genetic improvement or modification must be done in a spirit of fairness, equality and solidarity, in order to avoid discrimination and inequalities. Finally, the Australian report, which is the least talkative on the question, envisages a public consultation, but with the aim of making the scientific community and its actions transparent to the eyes of the Australian population.

The issue of governance and regulation is found in all the reports studied, with here again a few differences. The US and German reports both advocate collaboration, close cooperation between national and international institutions. A framework for the implementation of harmonized standards should lead to a convergence of national views (i.e., national laws and regulations, national academies of science and ethical councils, and international standards and regulations). The UK and Australian reports rely more on the existing national legal system. The UK reports, although they talk about an ethical and democratic governance, do not refer to a transnational vision that would supervise and advise the political, scientific and public stakeholders in the country. Likewise, discussions in the Australian report remain within the remits of the national legal system, suggesting a review of existing Australian regulations to take into account new methods of gene editing.

Some national reports mention subjects that we do (almost) not find in other reports, thus revealing some national specificities (which we will address in the next subsection, in our analysis of scientific articles). This is the case, for instance, of the Australian report, the only report to mention the benefits of gene editing in the fight against certain species of invasive plants and certain harmful insects (such as mosquitoes). The report also sees gene editing as a means of reducing the use of pesticides and thereby improving the quality of the environment and public health. The German reports, on the other hand, show a stronger focus on justice, equality, freedom and solidarity between individuals. It is argued that gene editing must be available to everyone, to avoid new discriminations. Finally, the UK reports evoke the consequences of gene editing on the economy and the market, with potentially new investments and funding streams and gains in productivity.

In conclusion, both the international summits and the national reports that we analyzed converge in a panoramic vision of the challenges of gene editing: they comprise precise descriptions of the scientific state of the art of the method and its different areas of application; they raise the issue of the kind and scale of governance needed; and they call for ethical and social dimensions to be taken into account. National specificities appear rather at the margins. In order to examine if and how these specificities are discussed and reflected in different countries, we now examine scientific articles.

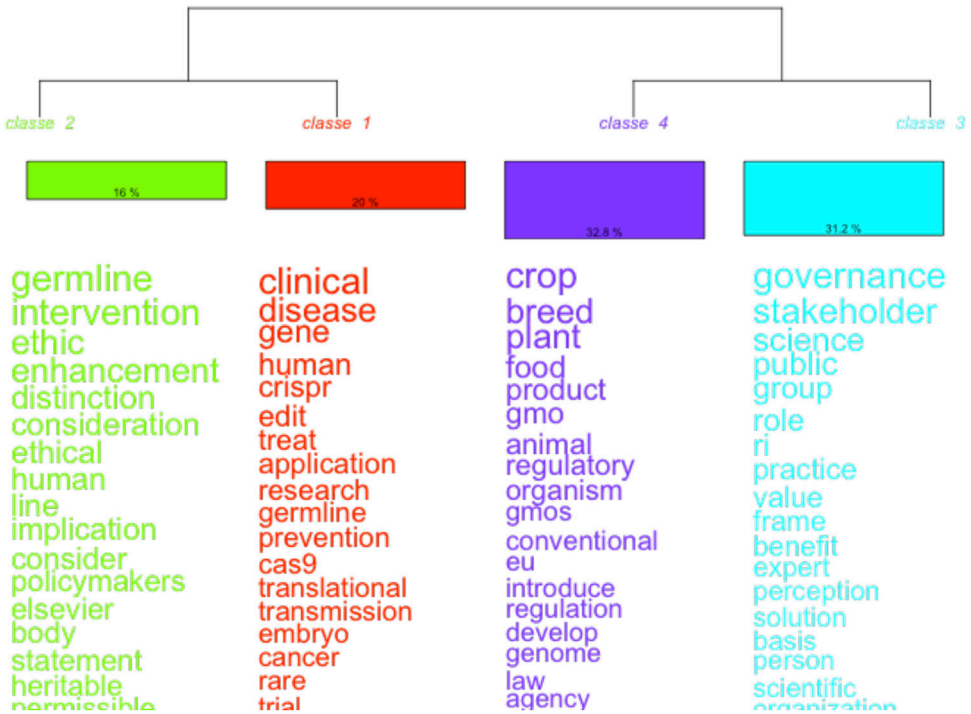

FIGURE 4 | Lexicometric analysis, *via* IRaMuTeQ, of the whole corpus of article abstracts (see **Supplementary File SA** for all IRaMuTeQ results) (*n* = 148). The given percentages refer to the size of the classes, expressed as a percentage of the classified corpus. In the text, we discuss them in descending order ("classe 4," then "classe 3," then "classe 1," then "classe 2").

Scientific Publications

In order to provide a general overview that can be compared to the above analysis of the summits and the reports, we assembled the abstracts of the 148 publications that we selected into a single corpus. The lexical analysis of this corpus reveals a classification into four main themes (see **Figure 4**).

The first theme revolves around the enhancement of existing crops or new varieties of genetically modified crops, new forms of animal breeding, and their impact on agriculture and human livelihoods, security and consumption: how will farmers adapt to new modes of production? Are GMOs the solution to food safety? Will consumer's preferences change regarding GMOs?

The second theme deals with the governance of gene editing, and the role of the public. National systems, transnational systems, institutions, scientific organizations, and the public face different options, interests and values that should be brought together *via* new forms of interaction. Terms such as "responsible innovation," the "precautionary principle," "debate" and "discuss" reveal that the debate around gene editing should take place in a more open and transdisciplinary way, by involving various stakeholders and members of the public. What is at stake here is the inclusion of lay expertise as a supplement of established scientific expertise [a theme discussed by a number of science studies scholars, including Callon (1999) and Epstein (1995)].

The third theme revolves around the technological advances that gene editing represents when applied to medicine, gene therapy, the prevention and treatment of rare genetic diseases or cancers.

Finally, the fourth theme reflects the "legal and ethical challenge" posed by human enhancement using gene editing. Whether or not to cross the "red line" of modifying the human genome, and thus interfere with the genetic heritage, is a fundamental issue that lies at the heart of lawmakers' and policymakers' concerns. These questions also confront the autonomy of parents regarding their choice to resort, or not, to the editing of a child's gene. A "societal, ethical and scientific debate," as well as the development of "ethical standards" must be, so the argument goes, the goal sought by institutional, scientific and societal stakeholders. The second and fourth themes reflect some of the most visible tensions and frictions in the recent controversy around human gene editing, that is, the discussion about "where to draw the line" and what choices to make when it comes to using gene editing for therapeutic purposes, or even for enhancement.

This is the general overview of the themes discussed by the scientific authors of our corpus, without distinction of national origin. Unsurprisingly, we encounter the themes addressed in the summits and the reports: the hopes created by the technology for the treatment of certain diseases, the development of more resistant and productive plants, governance issues and the role of the public. The description of the method and its targets also remains present. But a difference is nonetheless visible: the

publications discuss more concrete applications of gene editing (i.e., specific diseases or certain edible plants).

Benefits and Concerns Discussed

We subsequently separated the articles according to the countries of academic affiliation of their authors. Most authors underline the benefits that gene editing can generate. But there are notable differences depending on the country of academic origin of the authors. If we look at individual countries, we observe that UK authors highlight the advances regarding the autonomy of reproduction due to the possibility of modifying and improving embryos and US authors underline the possibility to fight against some of the consequences of climate change, in particular drought tolerance.

If we look at groups of countries, we see a reflection that is focused on gene or medical therapies (Canadian, Australian, Japanese and US authors), on certain rare genetic diseases, complex diseases or cancers (Australian, Canadian, US, and Japanese authors) and on fertility, reproduction and parenthood (Canadian and US authors). Some articles refer to the dignity and fundamental human rights at stake. Likewise, many publications in our corpus evoke the progress made (and to come) regarding plants and animals. These advances, described as the "fourth agricultural revolution" (by a UK author) or a "revolution" (German authors) are considered as significantly promising in terms of food security (Chinese authors) and the source of further innovations to come (German authors). While we see that the benefits of gene editing are discussed across countries, there are differences in terms of *what benefits* in particular gene editing might yield.

As much as different kinds of benefits are discussed in the publications, so are concerns. These concerns can be qualified as general and ubiquitous, since we find them almost uniformly shared in the articles we have studied. There are warnings about the risks of an uncontrolled deployment of gene editing in humans, but also in plants and animals. The technique remains ethically "controversial" and "immature" (Chinese authors). The potential risks to be mastered with regard to safety and human health (Australian, UK and Japanese authors), as well as for the safeguarding of wildlife, in particular due to uncertainties and risks regarding the "safety" of the method (Canadian and German authors), are seen as decisive for a large-scale dissemination and application of the technology. Some authors pay special attention to the "future generations" (Australian and German authors) - German authors being in line here with the German report's focus on "social justice." It is thus argued that as of today, societies must equip themselves with tools to measure the "risks" (German and Japanese authors), and take into account "uncertainties" (German authors) to remove the threat to human health posed by the new method. Such a framing of science in terms of benefits and risks has been criticised by a number of scholars and actors, for it narrows down the issue to a very technological and scientific debate at the expense of a wider, more social and democratic debate (Wickson and Wynne 2012; Helliwell et al., 2019).

Governance and its Geographies

Given these concerns and benefits, how is gene editing to be governed? All the authors in our corpus recognize the need to build a framework, whether an ethical, legal and/or moral one. But how should the geographical frame of this framework be defined? Should it be national, transnational, and/or international?

Unsurprisingly, He's announcement of the birth of the twins Lulu and Nana, whose genome was altered *via* gene editing, is discussed in many publications. It is argued that this event has raised the question about "where to draw the line" (Australian authors), putting to the test the old model of GMO regulation (UK, German, Australian and Chinese authors) that most countries or unions of countries have historically adopted. In order to respond to this problem, certain publications favor the implementation of the "precautionary principle" (Australian authors), considered as the prerequisite of moral responsibility and making it possible to manage a potential threat in a situation of uncertainty. As such, the European model of the precautionary principle is often cited as an example, as is the 2018 ruling of the EU Court of Justice (which states that products resulting from gene editing are considered as GMOs).

The European framework makes it possible to impose a certain number of rules on its member states. Concerning those nations not integrated within larger unions, it is argued that it is important that they develop their own existing legal frameworks which are sometimes considered obsolete, and put to the test by the rapid evolution of innovations in biotechnology (UK and Canadian authors) and work within a framework of "responsible innovation" (UK and US authors). The UK authors of our corpus join the vision that emerged from the UK and Australian reports analyzed previously: it is preferable to develop the existing national legal framework first, before agreeing at the international level. However, many authors of our study insist on the fact that regulation and governance need to happen on an international level - "international" and "global" are the geographical terms with most occurrences in our corpus (see **Table 4**). Such a "global" (Japanese authors), "international" (German authors), or "transnational" (Canadian authors) framework would be the response to a society and a policy that have also become global (Japanese authors) - and an international harmonization of legal standards is needed (German authors). It is argued that China needs to develop its own regulations in coordination with other countries (Canadian authors). The discussion also insists on the importance of scientific organizations, who should adopt a sort of political management of risk and should also seek for coordinated action at the transnational level (Canadian, UK and German authors).

If we analyse the active forms with most occurrences in our corpus, we see that three families of geographical terms are prominent: 1) the international level (with terms such as "international," "global," "world," "worldwide," "transnational"), 2) the national level (with "national," "country," "United Kingdom," "China," "Chinese," "American," "Nation"), and 3) Europe ("EU," "European," "Europe") (see **Table 4**). In addition, there are also

TABLE 4 | Active forms about space/geography with their occurrences.

Global 28; International 26; EU 23; National 18; World 15; Line 12; European 11; United Kingdom 11; Country 10; China 10; Chinese 9; Barrier 7; Europe 6; Transnational 6; Worldwide 5; Space 5; American 4; Nation 3; Boundary 3; Landscape 3; Internationally 3; Globally 3; Border 3; Americans 3; Australia 3

geographical terms in our corpus that are used in more metaphorical ways, such as line, barrier, space, and landscape. It is interesting to note that each of these terms is used in specific ways. The term line is used - apart from its occurrence in the "germline" and expressions such as "in line with" or "lines of inquiry" - to talk about legality and ethics: a "line" that is "drawn" and should "not be crossed" between editing somatic cells and editing the germline. The term barrier is often used to talk about socio-economic issues ("trade barriers," "diplomatic barriers"), while landscape is above all used to talk about the regulation of gene editing (the "regulatory landscape," seen as "complex," "mosaic," and "diverse"). Finally, space is mostly used to refer to public debate and democracy. We see here that multiple scales are at stake and that even the choice of words to describe the cultural spaces of gene editing need to be situated and contextualized. Science is not only produced and negotiated in space–a now common theme running through science studies–it is also governed and debated across diverse, multi-layered and fragmented spatialities.

Positioning the Public

The public is sometimes constructed in a rather narrow way. For instance, it is described as "recalcitrant" by US, UK and German authors. Terms such as "acceptance" (10 occurrences), "acceptable" (10), "accept" (9), and "acceptability" (4) are used and the perceived challenge is to educate, inform and convince the public of the positive features of gene editing. We have argued elsewhere that, in papers by Japanese authors for example, the public is referred to as an actor that "must accept" (Meyer 2020). Such a positioning stands in stark contrast to a vision of the public that is not perceived as ignorant or irrational but as an entity to be consulted. This finding is particularly noteworthy, since despite many calls for a rethinking and involvement of the public–and even the presence of papers by science studies scholars in our corpus–the public is still often portrayed as an actor that needs to accept scientific progress.

However, most authors condemn a conception of gene editing that does not consider the importance of the role of political and scientific governance. The need to involve civil society in the establishment of a public debate is underlined, in order to build an ethics around collectively accepted principles [visible through terms such as "involve" (15 occurrences), "engagement" (13), "engage" (11), and "dialogue" (2)]. In order to create such a democratic debate (US authors), the publications we have studied advocate for a greater integration of the public and of NGOs (UK authors), for increasing the engagement and participation of actors in ongoing debates (Canadian, UK and Japanese authors), for creating spaces for exchange (US authors) to facilitate discussion and develop interactions (UK authors) and find a consensus (Japanese authors) between experts and lay people.

Such a consideration for the public is not uncommon today; scholars have observed that decision-making processes within institutions and governments have significantly opened through public engagement and participation (see Irwin 2006; Chilvers and Kearnes, 2015). This new and more inclusive form of governance promotes a more active role for the public. Many actors have thus called for public debate on gene editing, be it the WHO, the UK Nuffield Council on Bioethics, or various other scientific institutions and academies.

DISCUSSION

This article has traced the contours and dynamics of the debates about the politics of gene editing by providing both a quantitative and qualitative analysis of the publications on the topic. Our scientometric analysis of scientific articles published between 2013 and 2020 shows that the governance and regulation of gene editing is discussed across an increasing range of disciplines and countries over the years. More disciplines become involved, with fewer articles in biology journals and a recent increase of articles from the social sciences. During the same period, the debate becomes more international, with proportionally fewer articles from North America and the number of contributing countries being multiplied by 9.5. Despite this opening up, discussions are still predominantly located in Europe and North America and in a few key domains, such as biology, genetics and the social sciences.

If we look at the content of the publications, be it scientific publications or reports, we observe a striking homogeneity. Several themes are recurrent, such as ethics, governance, and public debate. The general framing of the debate about the politics of gene editing is something almost universally shared. Within this frame, the benefits and risks of gene editing are discussed at great length. But while the benefits of gene editing are addressed across all the countries we studied, the specific kinds of benefits being discussed differ. The same counts for risks: while they are addressed in all the countries of our corpus, the ways in which they are approached does differ - with for instance some countries being more precautious than others.

We have refrained in this article from doing a strict comparison between countries. This would have led to two key shortcomings: we would have essentialised countries and have been tempted to provide cultural explanations for the differences observed; and our analysis would only have travelled *between countries*, but not *within our corpus*. What we have done was to trace the different kinds of arguments present, and how and where they are articulated. Importantly, this has enabled us to shed light on the different geographical scales mobilised in discussions.

Several spatialities are visible in our corpus: the international level, the European Union, as well as individual nations. Accordingly, we have seen calls for "coordination" and "dialogue" among and across these different spatialities. At the same time, we have also seen that coordination might be difficult to achieve, given differences across countries and continents. But not only are there differences among countries in terms of their regulatory frameworks and modes of governance. Our analysis also points to "power" differentials between countries, with a relatively small number of countries and groups of countries that lead the debate - be it in terms of scientific output, reports or the times they are referred to. The United States, the United Kingdom, and Europe clearly stand out. The other country that stands out, albeit in a rather negative way, is China, mostly *via* discussions around He's experiments.

Our main contributions are the following ones. We offer the first lexicometric analysis of publications about gene editing, and, together with other contributions in this special issue (i.e., Kuzma and Cummings), we offer some of the first quantitative analyses of the topic. Our analysis shows that across the countries we studied there are, all in all, only a few differences in terms of how gene editing is discussed. The general framing of the debate is widely shared (further academic work might look at why this is the case, and scientists role in this). The differences that we have observed are rather marginal and specific ones, when the applications or benefits of gene editing are discussed, or when the importance of the economy or of involving the public is mentioned. We also contribute to the geography of science and science studies by researching the spatiality of science in a multi-layered way. We have relied on a traditional geographic approach by analysing publications across the national affiliations of authors; we have traced the spatial terms that are mobilised and how they are used; and we have looked - in a more sociological reading of space - at the ways in which debates are framed and publics are positioned. We hold that bringing together multiple methods allows us to discuss the politics of gene editing in a richer and more multifaceted way, and that this opens up fertile dialogues between geography, sociology and political science.

Our findings are of course limited by our research design. We have analysed, *via* one open source program, the publications present in the Web of Science and selected seven countries within our corpus. Further research could thus examine the topic by searching other databases (i.e., Scopus, PubMed), selecting other countries (i.e., countries from the Global South) and use other programs (i.e., Hyperbase, TXM, VOSviewer) to do other kinds of analyses. Further research could also expand our research questions by analysing in more detail *who speaks* (what kinds of scientists, institutions, groups or committees are visible and/or authoritative in the debate - and how are they linked?) and how expertise is made, distributed and demarcated. We hold that the governance and regulation of gene editing is a fruitful terrain to be further explored in an empirical and interdisciplinary way and by bringing together qualitative and quantitative approaches.

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

MM contributed to the conception and theoretical problematization of the article and carried out the qualitative analysis. FV collected the data on scientific publications, while MM collected the data on reports. FV conducted the statistical and lexicometric analysis. FV and MM interpreted the scientometric results and FV interpreted the lexicometric results. MM wrote the first draft of the manuscript. All authors approved the submitted version.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpos.2021.731496/full#supplementary-material

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frontiers in Political Science

CONCEPTUAL ANALYSIS
published: 27 January 2022
doi: 10.3389/fpos.2021.793134

Deciphering the Fragmentation of the Human Genome Editing Regulatory Landscape

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Genome editing techniques have generated a growing interest following the discovery of the so-called CRISPR-Cas technique. It has raised a global uproar as regards its use in humans, especially after the 2018 announcement of a Chinese scientist who had used CRISPR to edit the genes of twin embryos. Indeed, one of the greatest concerns, although not the only one, has been the use of genome editing technologies to modify the human germline. In such scientific and technological context, the law plays a key role in framing what should be allowed or prohibited, and under which conditions, to find a balance between safe and accessible innovative treatments and respect of fundamental rights in accordance with the societal values and choices. Within the European Union, several institutions have considered the issues raised by human genome editing, and several legal texts participate in the establishment of the European regulatory framework applicable to human genome editing. Yet we argue in this article that the established regulatory landscape is fragmented in the sense of being divided, split, or segmented. Such fragmentation, which may have been inevitable for historical and technicolegal reasons, produces effects regarding the role of the current regulatory frameworks applicable to human genome editing. Focusing on the European Union and on the French levels of governance, we discuss how such fragmentation takes place through the identification of determinants of the human genome editing fragmented regulatory landscape. We argue that it should be seen as a process providing more contingent responses to human genome editing reflecting changing political and legal contexts.

Keywords: human genome editing, European Union law, French law, fragmentation, regulatory landscape

OPEN ACCESS

Edited by:
Alberto Asquer,
SOAS University of London,
United Kingdom

Reviewed by:
Andrea Boggio,
Bryant University, United States
Marton Varju,
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Specialty section:
This article was submitted to Politics of Technology, a section of the journal Frontiers in Political Science

Received: *11 October 2021*
Accepted: *13 December 2021*
Published: *27 January 2022*

Citation:
Mahalatchimy A and Rial-Sebbag E (2022) Deciphering the Fragmentation of the Human Genome Editing Regulatory Landscape. Front. Polit. Sci. 3:793134. doi: 10.3389/fpos.2021.793134

INTRODUCTION

Genome editing techniques have generated a growing interest following the discovery of the so-called CRISPR-Cas ("Clustered Regularly Interspaced Palindromic Repeats–Cas") technique (Hsu et al., 2014). It has raised a global uproar as regards its use in humans, especially after the 2018 announcement of a Chinese scientist who had used CRISPR to edit the genes of twin embryos (Greely, 2019). Indeed, one of the greatest concerns, although not the only one, has been the use of genome editing technologies to modify the human germline (Almqvist and Romano, 2020). In such scientific and technological context, the law plays a key role in framing what should be allowed or prohibited, and under which conditions, to find a balance between

safe and accessible innovative treatments and respect of fundamental rights in accordance with the societal values and choices. Whereas several initiatives have aimed at providing ethical and policy-oriented guidance,[1] it is the role of the law to adopt the binding rules to support such innovation and to determine the technological limits of what is acceptable for a society. Nevertheless, formal law is not a stand-alone norm to orient societal conducts, and it is tightly related to evolving political contexts. Indeed, we will show below that several organizations have considered the issues raised by human genome editing and several "norms," here understood as encompassing both formal law and regulations, and texts from nonlegal organizations aiming at regulating societal conducts, participate in the establishment of the European normative framework applicable to human genome editing within the European Union (EU). The EU level of governance is particularly interesting to explore as it has emerged as a legal and policy domain in the field of health law and policy (Guy and Sauer, 2017). It is also the most advanced legal system aiming at interstate collaborations, ranging from mere cooperation to harmonization, with binding jurisdictional mechanisms for implementation and interpretation of the law (Rieder, 2017).[2] As we will see below, EU law is far to be exempted from legal considerations on human genome editing, although this level of governance has often been overlooked in the literature. Indeed, much attention in legal scholarship was first given to national levels, often in a comparative approach (Araki and Ishii, 2014), or to the international level (Rosemann et al., 2019), including linking human rights law and biotechnologies (Francioni, 2007; Murphy, 2009). Nevertheless, a developing literature already explains how EU law applies throughout the development pipeline for new technologies more generally (Flear, 2017). More specific articles now discuss the current regulatory European framework (EU and Council of Europe levels)[3] on human germline modification (Almqvist and Romano, 2020; Nordberg et al., 2020), the focus of EU legislations on technical risks (Mahalatchimy and Rial-Sebbag, 2020), or the imaginary built into its framing (Mahalatchimy et al., 2021).

Building on this literature, we argue in this article that the established regulatory landscape is fragmented in the sense of being divided, split, or segmented. The phenomenon of fragmentation of the law (dispersal) is particularly discussed in international law. Usually, discussions start from the assumption that fragmentation must be occurring and then primarily tackle the problems it creates (Martineau, 2015). In contrast, we can consider fragmentation as a process that provides more contingent responses to human genome editing reflecting changing political and legal contexts. We will focus on how fragmentation is occurring at the EU level,[4] and we will take French law as a case study (Blasimme et al., 2020; Rial-Sebbag, 2020)[5] of implementation of EU law, including the last developments adopted from the French Bioethics Law (lastly revised in August 2021).[6] We will discuss three aspects of this regulatory landscape's fragmentation. The first aspect is the territorial fragmentation occurring within the European regulatory landscape on human gene editing. Indeed, this landscape is constituted by both EU law and national Member State laws. Through the case study of French law, we will highlight which considerations of human genome editing are regulated by EU and French laws and why. The second aspect is the substantive fragmentation that occurs within the law applicable to human genome editing. Indeed, several legal instruments constitute this regulatory framework. They relate to the regulated objects (tissues and cells, genetically modified organisms [GMOs], advanced therapy medicinal products), the stages of development of medicines based on human genome editing (fundamental research, patentability, clinical trials, marketing authorization), or the regulated field (civil law, public health law, Bioethics Law). The third aspect is the institutional fragmentation of the European regulatory landscape on human gene editing. Here we will show that activities on human genome editing are governed not only by French state and EU institutions, but also by European organizations that represent specific communities. It involves a set of rules with various authoritative weights. In the last part, we identify determinants of the human genome editing fragmented regulatory landscape that contribute to fragmentation as a process to adapt to the changing political and legal contexts.

TERRITORIAL FRAGMENTATION

The European regulatory landscape on human genome editing is fragmented at the territorial level. Such fragmentation comes from the legal status of the EU itself that has evolved from the

[1]See as an example the "Human Genome Initiative" set up under the umbrella of The National Academies of Sciences, Engineering, and Medicine, https://www.nationalacademies.org/our-work/human-gene-editing-initiative (last accessed November 17, 2021).

[2]Both actual litigation and the "shadow of litigation," which may be important, have to be taken into account.

[3]Even though out of the scope of this article, we recall that the Oviedo Convention bans interventions aiming at human germline modification and limits the purposes of any intervention on the human genome, including in the field of research, to prevention, diagnosis, or therapy according to its article 13: "An intervention seeking to modify the human genome may only be undertaken for preventive, diagnostic, or therapeutic purposes and only if its aim is not to introduce any modification in the genome of any descendants." The Committee on Bioethics of the Council of Europe has established a drafting group in order to "provide clarifications on the terms "preventive, diagnostic, and therapeutic" and to avoid misinterpretation of the applicability of this provision to "research." Council of Europe, Committee on Bioethics, 18th meeting, June 1–4, 2021, DH-BIO/Abr RAP18. France has signed (1997) and ratified (2011) this convention producing direct effects in its national legal framework.

[4]We are not covering in this article the links between EU law and international law (for instance the Oviedo Convention) because of the limited space and the specificity of the legal principles and mechanisms involved.

[5]For articles fully dedicated to the French frameworks.

[6]Law n°2021-2017 of 2 August 2021 on Bioethics, OJ n°0178 of 3 August 2021, text n°1.

funding treaties to the current applicable and so-called "Lisbon Treaty" including both the Treaty on the Functioning of the European Union (TFEU) and the Treaty on the European Union. First, the EU is organized in accordance with a legal sharing of competences between the EU as an organization and its Member States. Such sharing relies generally on four types of competence: exclusive EU competences, complementary EU competences, shared competences between the EU and its Member States, and exclusive Member States competences (Konstadinides, 2018). The areas the most relevant to human genome editing belong to the shared competences between the EU and its Member States or to the complementary EU competence regarding internal market, research, and public health. Consequently, EU and national laws have to adapt and to interact according to their competencies. The protection and improvement of human health are an area of primary national competence where the EU can only act according to its complementary competence,[7] meaning that the EU can only intervene to "support, coordinate, or supplement the actions of the Member States, without thereby superseding their competence in these areas" and that legally binding EU acts "shall not entail harmonization of Member States' laws or regulations."[8] However, the EU competence in public health has been strengthened (Hervey and McHale, 2015; Guy and Sauer, 2017), and it also includes now the shared competence in some common safety concerns in public health matters[9] where both the EU and its Member States are able to legislate and adopt legally binding acts: Member States exercise their own competence to the extent that the EU has not exercised or has decided to cease exercising its own competence.[10] According to the latter, the EU can adopt regulations in order to ensure "a high level of human health protection,"[11] which has often been combined with the achievement of the internal market,[12] the "protection of human health" having to be taken into account in all EU policies and activities.[13] The EU competency in research has also evolved as a specific shared competence (De Grove-Valdeyron, 2018) as long as its exercise "shall not result in Member States being prevented from exercising [their competences]."[14] This mechanistic approach on "who does what" could lead to a reduced vision on how the EU has used these legal bases to intervene in the field of health. In particular, article 114 TFUE has served as a (too) broad basis for the EU to legislate on numerous and various technologies with a focus on their commercial potential and their risks according to economic and political interests especially during the 1980s and 1990s (Hervey and McHale, 2015, 34–40). This has led to an extended framework for emerging technologies in health at the EU level, which has nevertheless been restrained by the limited EU competencies for other objectives than the internal market, especially as regards public health and research. Therefore, national laws remain primary regarding some aspects of new health technologies, including human genome editing techniques, in particular regarding the moral imperatives related to innovations, whereas EU law is clearly dominant to regulate these techniques for commercial objectives. Thus, these legal mechanisms reflect the role of the regulation in balancing the support to the development of technical advances in health and the management of their potential risks (technical and societal) for European citizens at European and national levels in accordance with various objectives. Although the resulting legal environment appears complex and sometimes unclear or even hazardous for technology developers as well as for citizens, it also highlights how fragmentation of applicable laws allows to take into account the political context of the EU governance of technology and its dynamics, such as the evolution of the sharing of competences between the EU and its Member States.

Consequently, the European regulatory landscape on human genome editing is territorially fragmented as it is constituted both by EU law that is implemented similarly in all EU Member States and by various national Member States laws. Through the case study of French law, we will highlight which considerations of human genome editing are regulated by EU and French laws and why. Here the laws distinguish human genome editing for research and for therapy (Mahalatchimy and Rial-Sebbag, 2020).[15]

Regarding human genome editing for research, fundamental and clinical research relies on different legal frameworks. While fundamental research is mainly regulated by national laws and accessorily by EU law, it is the contrary for clinical research. As long as genome editing technologies involve that human biological samples are to be used, the legal framework regarding fundamental research relies, first, on French law[16] for the collection of the samples and, second, on EU law for the safety rules.[17] This combination implies that researchers have to comply with the respect of individual fundamental rights as stated in the French legal framework and that the laboratories fulfill common EU safety requirements.

Regarding human genome editing for therapy, EU law is dominant regarding medicinal products based on human genome editing techniques, manufactured at the industrial scale and intended to be placed on the EU market. Indeed, the specific and unified legal regime established by Regulation (EC) n°1,394/2007 on Advanced Therapy Medicinal Products (ATMPs) applies.[18] However, where the medicinal products

[7]Article 6 TFEU.
[8]Article 2§5 TFEU.
[9]Article 4 TFEU.
[10]Article 2§2 TFEU.
[11]Article 168, TFEU.
[12]Article 114, TFEU.
[13]Article 168§1 TFEU.
[14]Article 4§3 TFEU.

[15]For an article providing a detailed analysis of how EU law regulates human genome editing for research and therapy.
[16]Law on research involving human person (2012) and Bioethics Law for research on embryos (2021).
[17]Mainly Directive 2004/23/EC of the European Parliament and of the Council of March 31, 2004, on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage, and distribution of human tissues and cells, OJ L 102, 7.4.2004, pp. 48–58, and its implementation directives of 2006 and 2015.
[18]Regulation (EC) n°1,394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) n°726/2004, OJ L324, 10.12.2007, p.121.

based on human genome editing techniques are "prepared on a nonroutine basis according to specific quality standards, and used within the same Member State in a hospital under the exclusive responsibility of a medical practitioner, in order to comply with an individual medical prescription for a custom-made product for an individual patient," they are regulated under national laws.[19] Moreover, where the products based on human genome editing techniques for therapy do not fall within the exact definitions of ATMPs, they are regulated at national levels if they are not manufactured at the industrial scale and not intended to be placed on the EU market. This dichotomy based on the clearly stated legal sharing of competencies between EU and its Member States has led to some blurring on how to identify the correct level of rules to be applied to genome editing techniques, creating some legal insecurity to the various stakeholders (Mourby and Morrison, 2020).

Thus, human gene editing technologies are regulated both by EU law and national laws, and as such, the regulatory landscape is territorially fragmented.

SUBSTANTIVE FRAGMENTATION

The second aspect is the substantive fragmentation that occurs within the law applicable to human genome editing. On the one hand, substantive fragmentation is the direct consequence of territorial fragmentation as it has been explained above regarding fundamental and clinical research, for instance. On the other hand, the legal landscape of human genome editing is also fragmented substantively at the EU level as long as there is currently no common and explicit EU legal approach on genomics[20] and on human genome editing. Nevertheless, several European legislations provide legal frameworks applicable to human genome editing.

First, the EU's Legal Protection of Biotechnological Inventions Directive[21] (Biotechnology Directive) allows to obtain a patent for inventions based on biological elements where three main criteria are met: the invention is new, it involves an inventive step, and it is susceptible of industrial application.[22] In this context, the isolation or production by means of a technical process of a product consisting of or containing biological material, such as the sequence or partial sequence of a gene, may be a patentable invention, even if the structure of that element is identical to that of a natural element.[23] Nevertheless, "the human body, at the various stages of its formation and development, and the simple discovery of one of its elements, including the sequence or partial sequence of a gene, cannot constitute patentable inventions."[24] Consequently, inventions based on human genome editing techniques are patentable under EU law. However, two main exclusions limit the extent of their patentability.

The Biotechnology Directive provides for moral and ethics exclusions to the patentability of biotechnological inventions where their commercial exploitation would be contrary to "order public or morality."[25] Within the nonexhaustive and indicative list of processes to which the exclusion from patentability applies, all items are relevant to genome editing. The first two ones are directly related to human genome editing as they mention "processes for cloning human beings"[26] and "processes for modifying the germline genetic identity of human beings" (Li, 2014; Wong and Mahalatchimy, 2018; Mahalatchimy et al., 2021).[27] The last two ones are indirectly related to human genome editing. Indeed, the exclusion of the "uses of human embryos for industrial or commercial purposes"[28] introduces additional limits to genome editing on human embryos that go beyond the modification of the human germline genetic identity. As such, it limits the patentability of inventions based on genome editing in human embryos at a later stage of their development as long as the "prior destruction of human embryos or their use as base material, whatever the stage at which that takes place" excludes an invention from patentability.[29] Finally, the exclusion of "processes for modifying the genetic identity of animals, which are likely to cause them suffering without any substantial medical benefit to man or animal, and also animals resulting from such processes" limits the patentability of these inventions at the preclinical stage of gene editing technologies' development. The Biotechnology Directive also provides for a medical treatment exclusion as long as it excludes from patentability "methods of therapeutic, diagnostic and surgical treatment on the human or animal body."[30]

Beyond these main rules, the patent regulatory landscape is complex as highlighted by the battles of priority and claims regarding patents linked to CRISPR-Cas9, and opposing mainly the University of California (UC) together with the University of Vienna (referred to as CVC), and the Broad Institute in Cambridge (the Broad), Massachusetts, both in the United States and in Europe. While UC claims patent rights for the uses of CRISPR in all types of cells, the Broad claims them for their uses in eukaryotes, a key area to develop human medicines. Although the battle is still ongoing (Cohen, 2020), the United States Patent and Trademark Office seems to have ruled more in favor of the Broad, but it seems to be the opposite for the European Patent office (Cohen, 2017a). Nevertheless, the issues at stake on overlapping or shared patent rights are wider (Feeney et al., 2018), notably as they involve other parties that have filed early CRISPR claims with patent offices (Cohen, 2017b).

[19]Recital (6) and article 28.2 of Regulation (CE) n°1,394/2007.

[20]JRC Science for Policy Report, Overview of EU national legislation on genomics, 2018, p. 74.

[21]Directive 98/44/EC on the Legal Protection of Biotechnological Inventions, OJ 1998 L 213/13.

[22]Article 4 Directive 98/44/EC, *ibid*.

[23]Article 5 (2) Directive 98/44/EC, *ibid*.

[24]Article 5 (1) Directive 98/44/EC, *ibid*.

[25]Article 6 Directive 98/44/EC, *ibid*.

[26]Article 6(2) (a) Directive 98/44/EC, *ibid*.

[27]Article 6(2) (b) Directive 98/44/EC, *ibid*.

[28]Article 6(2) (c) Directive 98/44/EC, *ibid*.

[29]CJEU, Grand Chamber, Brüstle v Greenpeace eV (C-34/10) [2011] E.C.R. I-9821 [2012] 1 C.M.L.R. 41, at 52.

[30]Recital 35 Directive 98/44/EC, *ibid*.

Second, two main EU legal instruments apply to research on human genome editing techniques. Research on human genome editing techniques can be funded by the EU as long as it complies with the current Framework Programme for Research and Innovation for 2021–2027, "Horizon Europe."[31] On the one hand, it shall comply with "ethical principles and relevant national, Union, and international legislation, including the Charter of Fundamental Rights of the EU and the European Convention on Human Rights and its Supplementary Protocols."[32] On the other hand, it excludes from funding "activities intended to modify the genetic heritage of human beings, which could make such modifications heritable"[33] as well as the funding of research that is prohibited in all Member States or in a Member State where such research activity is forbidden.[34] On such legal basis, "EU has funded research projects across genome editing technologies, in particular in the biomedical sector" but also in agriculture, ecosystems, and insects.[35]

Moreover, the clinical trials regulation[36] applies to medicines based on human genome editing techniques, especially regarding advanced therapy medicinal products,[37] and provides the same requirements as for any other medicinal products in order to generate "reliable and robust data."[38] Safety in clinical trials stems from the investigational medicinal product and the intervention[39] that are assessed by national competent authorities and ethics committees in order to authorize the start of the clinical trials. The only specificity mentioned by this regulation regarding clinical trials of advanced therapy medicinal products concerns the period for producing this evaluation and the possibility for the reporting Member State[40] to extend it by a further 50 days for the purpose of consulting experts.[41] However, specific Good Clinical Practice applies to advanced therapy medicinal products.[42] Neither these guidelines nor the report of the EMA expert meeting on genome editing technologies used in medicinal products provides for specificities regarding clinical aspects due to insufficient clinical evidences.[43]

Most importantly, the clinical trials regulation prohibits to carry out "gene therapy clinical trials, which result in modifications to the subject's germline genetic identity."[44] "As of March 2021, no clinical trials of *in vivo* genome editing are known to be underway in the EU but a few trials using *ex vivo* genome editing, to modify autologous cells, are reported in the EU Clinical Trials Register."[45]

Apart from the aforementioned European legal instruments providing rules for clinical research and research funding and by opposition to French law (see below), the EU has not adopted specific rules regarding the uses of biological samples in fundamental research[46] and *a fortiori* in the context of human genome editing. Nevertheless, the safety of human tissues and cells is framed by EU law by the Tissues and Cells Directives,[47] as long as they are used for human applications, such as graft or more widely therapy. Legally, these directives do not apply in research. Nevertheless, they guide the overall safety and health risk management expectations of establishments using human cells. As in practice, biobanks generally combined health safety and research objectives; they apply the higher safety standards provided by the European Directives on Tissues and Cells for their activities, be the tissues and cells used for therapy or for research.

Third, although there is no authorized medicinal product that use genome editing as of mid-2020,[48] therapies using genome editing techniques will be regulated by the European regulation on ATMPs,[49] as long as they fall under its scope as explained above in 2). This regulation is stricter in terms of risk assessment than that provided for other medicinal products, because of the innovative nature and the complexity of the manufacturing processes of ATMPs. It also provides regulatory incentives for their development and their market access, such as European Medicines Agency's fees reduction. In order for the European Commission to grant the authorization decision, ATMPs have to go through the centralized European Marketing Authorization procedure. This involves the opinion of the Committee for

[31]Regulation (EU) 2021/695 of the European Parliament and of the Council of 28 April 2021 establishing Horizon Europe—the Framework Programme for Research and Innovation, laying down its rules for participation and dissemination, and repealing Regulations (EU) No 1290/2013 and (EU) No 1291/2013, OJ L170 of 12.5.2021, pp. 1–68.

[32]Article 19§1 of Regulation (EU) 2021/695, *ibid*.

[33]Article 18§1 b) of Regulation (EU) 2021/695, *op. cit*. This article also excludes at §1: "a) activities aiming at human cloning for reproductive purposes" and "c) activities intended to create human embryos solely for the purpose of research or for the purpose of stem cell procurement, including by means of somatic cell nuclear transfer."

[34]Article 18§2 of Regulation (EU) 2021/695, *op. cit*.

[35]"There are about 200 EU projects in the CORDIS database containing "gene editing" in their description." European Medicines Agency and Heads of Medicines Agencies. Genome editing EU-IN Horizon Scanning Report, February 15, 2021, EMA/319248/2020, p. 10.

[36]Regulation (EU) 536/2014 on Clinical Trials on Medicinal Products for Human Use, and Repealing Directive 2001/20/EC, OJ 2014 L 158/1.

[37]An investigational medicinal product that is an advanced therapy medicinal product as defined by Regulation (EC) n°1,394/2007.

[38]Article 3b) of Regulation (EU) 536/2014, *op. cit*.

[39]Recital (11) of Regulation (EU) 536/2014, *op. cit*.

[40]The Member State designated to conduct the clinical assessment.

[41]Article 6§7 of Regulation (EU) 536/2014, *op. cit*.

[42]European Commission, Guidelines on Good Clinical Practice specific to advanced therapy medicinal products, October 10, 2019, C(2019) 7,140 final.

[43]EMA, *Report of the EMA Expert Meeting on Genome Editing Technologies Used in Medicinal Product Development* (2018), EMA/47066/2018.

[44]Article 90 of Regulation (EU) 536/2014, *op. cit*., which maintains this prohibition as established by previous Directive 2001/20/EC on the Approximation of the Laws, Regulations and Administrative Provisions of the Member States relating to the Implementation of Good Clinical Practice in the Conduct of Clinical Trials on Medicinal Products for Human Use, OJ 2001 L 121/34.

[45]European Medicines Agency and Heads of Medicines Agencies. Genome Editing EU-IN Horizon Scanning Report, *op. cit*. p. 4.

[46]Biobanks for Europe: a challenge for governance, Directorate-General for Research and Innovation (European Commission), https://op.europa.eu/en/publication-detail/-/publication/629eae10-53fc-4a52-adc2-210d4fcad8f2 (last accessed November 17, 2021).

[47]Directive 2004/23/EC and its implementation directives of 2006 and 2015, *op. cit*.

[48]European Medicines Agency and Heads of Medicines Agencies. Genome Editing EU-IN Horizon Scanning Report, *op. cit*. p. 4.

[49]Regulation (EC) 1,394/2007 on Advanced Therapy Medicinal Products and Amending Directive 2001/83/EC and Regulation (EC) 726/2004, OJ 2007 L 324/121.

Advanced Therapies, in addition to that of the Committee for Medicinal Products for Human Use, within the European Medicines Agency (EMA). Generally, safety requirements are strengthened, and specific guidelines related to good clinical, manufacturing, and pharmacovigilance practices apply. However, although it is very likely that therapies using genome editing techniques will be considered as ATMPs, it will be more challenging to determine in which type of ATMPs they will be classified into. Indeed, Mourby and Morrison have suggested that nucleic acids not produced by recombination, and protein-based molecules, which are also gene-editing techniques, may fall outside the scope of the definition of gene therapy medicinal products within the ATMP Regulation, which focuses on gene therapies containing or consisting of recombinant nucleic acid (Mourby and Morrison, 2020). Moreover, on the basis of existing scientific guidelines[50] we have previously explained that if cells that have been genetically modified by genome editing techniques are developed to use a targeted genetic sequence for therapeutic purposes, it should be a gene therapy medicinal product. However, if these cells are used for manufacturing purposes in the development of cell or tissue therapy, it should be a cell therapy medicinal product or a tissue-engineered product (Mahalatchimy and Rial-Sebbag, 2020).

Fourth, the legislations on GMOs[51] and genetically modified micro-organisms (GMMOs) apply.[52] Directive 2009/41/EC on the contained use of GMMOs applies to human genome editing techniques taking place in laboratories as long as these techniques fall into the scope of this directive. The latter is limited by the legal definition of GMMOs: "any microbiological entity, cellular or noncellular, capable of replication or of transferring genetic material, including viruses, viroids, and animal and plant cells in culture."[53] It is thus related to techniques using vectors. However, it is unclear whether the use of other genomic techniques in human genome editing is covered by this directive. Directive 2009/41/EC establishes risk assessment procedures according to four classes of GMMOs in order to obtain receipt or authorization of their contained use from the national competent authority. Directive 2001/18/EC on the deliberate release into the environment of GMOs provides a risk assessment methodology over time, based on principles to identify the negative impacts that the GMO release could produce.[54] The assessment aims to determine the GMO classification according to their level of risk concerning the security of the premises. Directive 2001/18/EC applies to edited human cells when the genetic manipulations carried out are those described by the directive in the legal definition of GMOs: "an organism, with the exception of human beings, in which the genetic material has been altered in a way that does not occur naturally by mating and/or natural recombination."[55] But the extent of the application of the said directive to human genome editing techniques and the modalities of its implementation remain unclear in two respects in particular. On the one hand, "human beings" are excluded from the legal definition of GMOs, as long as "genetically modified human beings" were unthinkable at the time of adoption of Directive 2001/18/EC. On the other hand, in Confédération paysanne and Others v. Premier ministre and Ministre de l'Agriculture, de l'Agroalimentaire et de la Forêt, the Court of Justice of the European Union rules out that organisms obtained by mutagenesis are to be classified as GMOs, as the genetic material of an organism is altered by the techniques and methods of mutagenesis in a way that does not occur naturally.[56] Therefore, the Court has clarified that genome editing techniques are covered by the directive in an extensive manner as not only the manipulations of transgenesis (insertion of a gene) are concerned but also those of mutagenesis. However, the latter case law applies only to the field of plants, and it remains uncertain this interpretation would cover the technique of mutagenesis applied to human genetic material. Clarification on such aspect did not occur within the European Commission's study, requested by the Council of the European Union,[57] on the status of new genomic techniques under EU law.[58] Nevertheless, the European Commission highlighted that the application of the GMO legislation to medicines, as it is for medicines based on human genome editing techniques, "hinders the development of these products in the EU."[59] Indeed, during a public consultation preceding this study, Member States and other stakeholders underlined challenges of applying the current GMO legislation to medicinal products for human use such as duplication of assessment by medicines and environmental agencies,[60] complex and lengthy process for gaining approval of clinical trials with products consisting of or containing GMOs,[61] and public information and understanding.[62] These issues have been referred back to the EU pharmaceutical strategy.[63] Hence, the European Commission will

[50]Mainly EMA, Guideline on quality, non-clinical and clinical aspects of gene therapy medicinal products, 22 March 2018, EMA/CAT/80183/2014; and EMA, Guideline on Quality, Non-clinical and Clinical Aspects of Medicinal Products Containing Genetically Modified Cells, November 12, 2020, EMA/CAT/GTWP/671639/2008 Rev. 1—corr.

[51]Directive 2001/18/EC on the Deliberate Release Into the Environment of Genetically Modified Organisms and Repealing Directive 90/220/EEC, OJ 2001 L 106/1.

[52]Directive 2009/41/EC on the Contained Use of Genetically Modified Micro-organisms, OJ 2009 L 125/75.

[53]Article 2§a of Directive 2009/41/EC, *ibid.*

[54]Annex II of DIRECTIVE 2001/18/EC, *op. cit.*

[55]Article 2§1 of DIRECTIVE 2001/18/EC, *op. cit.*

[56]Case C-528/16 Confédération paysanne and Others v. Premier ministre and Ministre de l'Agriculture, de l'Agroalimentaire et de la Forêt [2018] (ECLI:EU:C:2018:583).

[57]Council Decision (EU) 2019/1904 of November 8, 2019, requesting the commission to submit a study in light of the Court of Justice's judgment in Case C-528/16 regarding the status of novel genomic techniques under Union law, and a proposal, if appropriate in view of the outcomes of the study, JO L 293 du 14.11.2019, pp. 103–104.

[58]European Commission, Commission staff working document, study on the status of new genomic techniques under Union law and in light of the Court of Justice ruling in Case C-528/16, April 29, 2021, SWD (2021) 92 final.

[59]*Ibid.* p. 59.

[60]Europabio's answer to the Stakeholder Questionnaire on new genomic techniques to contribute to a commission study requested by the Council, May 15, 2020.

[61]Alliance for Regenerative Medicine's answer to the Stakeholder Questionnaire on new genomic techniques to contribute to a commission study requested by the Council, May 15, 2020.

[62]France's answer to the Stakeholder Questionnaire on new genomic techniques to contribute to a commission study requested by the Council, July 3, 2020.

[63]European Commission, Commission staff working document, study on the status of new genomic techniques under Union law and in light of the Court of Justice ruling in Case C-528/16, *op. cit.* p. 59.

explore solutions during the evaluation of the pharmaceutical legislation in 2022 in order to "consider adapting regulatory requirements in the pharmaceutical legislation, applicable to medicines for human use that contain or consist of genetically modified organisms."[64]

As a result, even if some rules are stated at the EU level, some of them remain unclear especially because of the little experience in the field and because of the fact that most of the legal requirements on the use of genome editing techniques are provided by national legislations.

At the French national level, the rules that apply to human genome editing are not embedded within one clear regulatory framework, and two pieces of legislation are concerned. The Bioethics Laws as adopted in 1994[65] aimed at enacting fundamental rights to protect the human body and its parts[66] and at applying these principles in medical and research practices.[67]

First, the core principles regarding the protection of the human genome are enacted in the Civil Code (CC). This code aims at regulating the status of individuals and their relationships. Since the adoption of the first Bioethics Laws as partly implemented in this code,[68] the CC also recognizes a status for the human species and their integrity.[69] Thus, genome editing techniques leading to any modification of the human genome that should be transmitted to the next generation is considered unlawful.[70] Second, the applications in health care are covered by the provisions of the Public Health Code (PHC), which is regulating the implementation of genetic technologies in alive humans and in embryos. The previous version of the Bioethics Laws (of 2011) had not identified genome editing as a key question because it was not so much developed at that time. Several provisions of the PHC[71] were in alignment with the ban of genome editing as stated in the CC where genome editing was supposed to be conducted as an intervention on embryos leading to birth. However, the provisions related to research activities in this field were unclear and the French legal framework was unable to secure the activities of French researchers. As a consequence, heated debates and controversies occurred during the revision process of the Bioethics Law recently published in August 2021 in order to clarify whether the ban of using genome editing techniques was only applying to therapeutic/diagnosis interventions in embryos or also to research activities.

To date, the legal provisions are clearer and should distinguish two main cases. The first refers to the use in research of genome editing techniques in alive humans to treat somatic cells. As long as this intervention is used only in somatic cells to treat a disease and cannot be transmitted to the offspring, it is qualified as a gene therapy. In this context, the research is lawful as long as the fundamental principles and procedures ensure the respect of voluntary participation and follow the rules attached to the collection, storage, and use of human biological materials as stated in the PHC. Clinical trials are also permitted under the umbrella of the European law (Clinical Trial Regulation and ATMP Regulation, see above). However, the genome editing regulatory landscape is even more fragmented when it comes to its use in embryos. The use of genome editing techniques in embryos and human embryonic stem cells (hESCs) is more problematic given the germline modifications involved. Despite quick references to hESCs in European law, the framing of their use occurs mainly in national regulations (Isasi et al., 2016). The adoption of the new 2021 Bioethics Law, after strong debates in the two parliamentary assemblies, clarified the legal landscape. As a result, according to the new article L2151-2 PHC, the ban to use heritable genome editing as a therapeutic intervention is maintained, but the research is now specifically allowed. This clear support to research activities results from the removal of the ban to create transgenic embryos as previously stated in the law.

The research protocol evaluation will be in the hands of the competent authority (Agence Nationale de Sécurité du Médicament et des produits de santé) and of the Research Ethics Committee (in France Comité de Protection des personnes) for research on somatic cells. The Biomedicine Agency (Agence de la Biomédecine) is the national competent authority for research on embryos and hESCs. They will be particularly in charge of compliance with safety requirements as stated in the European Regulations and fundamental rights as stated in the Bioethics Law.

Thus, the substantive fragmentation occurs both in EU and French laws as regards fundamental research and clinical research, research and therapy, or genome editing on somatic cells and on embryos and hESCs.

The fragmentation as observed regarding the territorial and substantive landscapes is also perceptible when it comes to institutions.

INSTITUTIONAL FRAGMENTATION

The third aspect is the institutional fragmentation of the European regulatory landscape on human gene editing.

[64]Communication from the Commission to the European Parliament, the Council, the European Economic and Social Committee and the Committee of the Regions, Pharmaceutical Strategy for Europe, November 25, 2020, COM (2020)761 final, p. 16.

[65]These laws were initially adopted in 1994 with a principle of periodic revisions that occurred in 2004, 2011, and 2021.

[66]Loi n°94-653 du 29 juillet 1994 relative au respect du corps humain (respect for the human body).

[67]Loi n°94-954 du 29 Juillet 1994 relative au don et à l'utilisation des éléments et produits du corps humain, à l'assistance médicale à la procréation et au diagnostic prénatal (donation and use of human body parts and products, medically assisted procreation, and prenatal diagnosis).

[68]The law n°94-653 has been implemented in the CC.

[69]Civil Code art. 16-4: No one may infringe upon the integrity of mankind. Any eugenic practice that aims at organizing the selection of persons is forbidden. Any medical procedure whose purpose is to cause the birth of a child genetically identical to another person alive or dead is forbidden. Without prejudice to research aimed at the prevention, diagnosis, and treatment of diseases, no transformation may be made to genetic characteristics with the aim of modifying the person's descendants.

[70]*Ibid.*

[71]Article L2151-2 PHC was banning the creation of transgenic and chimeric embryos, and article L2151-5 IV was banning the reimplantation of embryos after research for the purpose of giving birth.

Beyond the regulatory frameworks, strictly considered as "state law,"[72] which apply to human genome editing, several European organizations have highlighted the societal challenges and their related ethical principles regarding human genome editing.

Regarding the EU institutions, and beyond the aforementioned EMA's technical report, both the European Commission[73] and the European Parliament[74] have provided a state of the challenges raised by human genome editing. The European Group on Ethics in Science and New Technologies is the one that has gone deeper on these aspects with a 2016 statement[75] and a more complete 2021 opinion on the ethics of genome editing.[76] The Council of the EU has considered genome editing regarding GMOs in plants only in its request to the European Commission to conduct the study on the status of novel genomic techniques under Union law, with the latter sending back the issues to the EU pharmaceutical strategy as mentioned previously.

In parallel to the classical EU bodies, several European organizations that represent specific communities have gone beyond highlighting the societal challenges raised by human genome editing in providing recommendations. These organizations are the Federation of European Academies of Medicine,[77] the European Academies Science Advisory Council,[78] the European Society of Human Reproduction and Embryology, and the European Society of Human Genetics together (de Wert et al., 2018), and the Patients Network for Medical Research and Health.[79]

At the national level, here concerning France, both governmental institutions and other organizations have tackled human genome editing.[80] In addition to the clarifications adopted by the new French Bioethics Law[81] on which activities can be considered as lawful and which are still forbidden, medical institutions, namely, academia, as well as several ethics committees, have taken position (see below).

The parliamentary debates occurring during the revision process of the Bioethics Law[82] (2019–2021) show a strong opposition between the Senate and the National Assembly. The proposal of opening genome editing of embryos and hESCs to research activities was strongly supported by the National Assembly in the name of advancing science and of making innovations available to researchers. The arguments were developed on the ground of technology advancement, of benefit for knowledge, and, most of all, of keeping French research activities' competitiveness. On the contrary, the Senate based its reluctance on moral arguments, stating that opening these activities would favor human selection and would open rooms for eugenics. The last version of the law, as adopted by the National Assembly, was submitted to the Constitutional Council[83] after a referral from the Senate. In this decision, the Council states that according to all the requirements already enacted in the Bioethics Law regarding the authorization of the research protocols on embryos and hESCs, all the necessary safeguards[84] are in place to lawfully conduct this research and that this change of the law is not contrary to the respect of the human dignity principle.

Regarding academia, two main institutions (Academia of Medicine and Academia of Sciences) have elaborated statements, before the adoption of the Bioethics Law, then contributing to the debate. We can underline here that they were representing the voice of medical and scientific practitioners. The Academia of Sciences,[85] rather than providing a report or full statement regarding genome editing, organized several scientific manifestations or public events. Then, in its recommendations in the scope of the revision of the Bioethics Law,[86] they focused on the ethical and societal questions raised by genome editing in plants and in animals. However, after the twins' birth in China, the Academia of Sciences joined the Academia of Medicine to ban Dr He Jianku's initiative through the adoption of a joint declaration.[87] Both academia insisted on the lack of knowledge regarding genome editing uses in practice and added that "in the current state of knowledge, the conditions are not met to open the way to the birth of children whose genome has been modified in the embryonic state." Moreover, the Academia of Medicine issued a report in 2016 where academicians stated that "while avoiding the transmission of a genetic disorder to a child could be an acceptable indication for modification of the unborn child's genome, the conditions are currently far from being met for

[72]Although the European Union is a European organization and not a state, we use "state law" in the meaning of law established through a population-level democracy process.

[73]European Commission and European Group on Ethics, Open Round Table on the Ethics of Gene Editing, October 16, 2019: https://ec.europa.eu/info/events/round-table-ethics-gene-editing-2019-oct-16_en.

[74]European Parliament, What if gene editing became routine practice? October 16, 2018. https://www.europarl.europa.eu/RegData/etudes/ATAG/2018/624260/EPRS_ATA(2018)624,260_EN.pdf.

[75]European Group on Ethics in Science and New Technologies, statement on gene editing, 2016.

[76]European Group on Ethics in Science and New Technologies, Opinion n°32 on the ethics of genome editing, March 19, 2021.

[77]Federation of European Academies of Medicine. Human genome editing in EU, Report of a workshop held on April 28, 2016, at the French Academy of Medicine, 2016.

[78]European Academies Science Advisory Council (EASAC). Genome editing: scientific opportunities, public interests and policy options in the European Union. EASAC policy report 31, 2017.

[79]Patients Network for Medical Research and Health. Gene editing and the patient's perspective, 28 September 2017: https://egan.eu/news/gene-editing-and-the-patients-perspective/.

[80]We will highlight those that can be considered as the most representative.

[81]*Supra*.

[82]For a full picture of the process, see Senate's documentation, https://www.senat.fr/dossier-legislatif/pjl19-063.html.

[83]Decision of the Constitutional Council n° 2021-821 DC of July 29, 2021, available at https://www.conseil-constitutionnel.fr/decision/2021/2021821DC.htm.

[84]Such as a written protocol submitted to an independent Agency (Agence de la Biomédecine), the assessment of the scientific and ethics validity and the justification to use embryos or hESCs.

[85]https://www.academie-sciences.fr/fr/.

[86]https://www.academie-sciences.fr/fr/Rapports-ouvrages-avis-et-recommandations-de-l-Academie/revision-de-la-loi-de-bioethique.html.

[87]https://www.academie-sciences.fr/fr/Rapports-ouvrages-avis-et-recommandations-de-l-Academie/bebe-genetiquement-modifie.html.

such an approach to be clinically feasible."[88] Thus, rather than banning genome editing in embryos for moral reasons, the Academia built its argumentation on the lack of knowledge regarding the risks of implementing this new technology and identified several other options that would be available and lawful for couples to help them in their parental project (such as adoption, gametes donation. . .).

Finally, several ethics committees[89] expressed their concerns regarding the deployment of genome editing. We will insist on the opinion issued by the National Ethics Committee in France in 2019[90] in this regard. After providing background analysis of the scientific, legal, and deontological issues raised by genome editing in humans, the Committee acknowledged that genome editing contributes to the advancement of science, even when applied in embryos, but that strict attention should be paid to the potential consequences of its use for the human germline and on the environment. It also insisted on three major points that should be further considered: (1) what will be what the impact of these technologies regarding the societal expectations (unrealistic expectations)? (2) If implementing CRISPR-Cas9 in embryos for therapeutic purposes is forbidden in France, what if it is allowed in other European countries (medical tourism)? (3) How to ensure that genome editing will be regulated only for health purposes and not for weapon development (resistance to virus or bacteria)? The Council concludes that these issues call for more information and transparency, should be opened to a wide debate with the public, and should be limited through the frame of the Bioethics Laws and the Oviedo Convention. By the end, regarding genome editing in embryos, because of the uncertainties and the risks, it recommends a cautious approach based on a possible moratorium, but surprisingly, it also recognizes that "preventing such diseases (severe and incurable) from the embryonic stage, through targeted genome repair, justifies special ethical reflection on care that may constitute a possible medical approach in the future." This position, shared by other national ethics committees,[91] is thus a step to overcome the moral debate toward possibilities to use genome editing in embryos under strict conditions in the future. Other initiatives should also be considered such as the setting up of the Association for Responsible Research and Innovation in Genome Editing[92] that shows the necessary interplay between national and international governance of genome editing. The ethics committee of Inserm is at the initiative of its creation, but its scientific committee consisted of international members. Its ambition is to promote international and interdisciplinary collaborations to foster the development of genome editing techniques embedded in a safe ethical framework as well as supporting dialogue between the various stakeholders and to provide training.

Therefore, activities on human genome editing are regulated not only by French state and EU institutions, but also by European and French organizations that represent specific communities.

DISCUSSION

Through the fragmented regulatory landscape of human genome editing at the territorial, material, and institutional levels, several interdependent determinants of regulatory fragmentation can be identified.

First, regulatory fragmentation occurs according to the remit of each organization providing norms. Such determinant is particularly emphasized by the territorial fragmentation, which is mainly based on the sharing of competences between the EU and its Member States. Such fragmentation is increased by the mobilization of various competences (for instance, the shared and complementary competences in the field of public health) linked to different objectives (for instance, good functioning of the internal market, guarantee of a high level of protection of public health) and to various legal methods (for instance, harmonization, cooperation) and legal tools with various authoritative weights (i.e., regulation, directive, guidelines). The determinant of the remit of each normative organization also arises regarding the institutional fragmentation, where various organizations gain legitimization of their normative power either from the classical democratic process (for legal institutions such as those of the EU and of the Member States) or from the communities they represent (mainly scientific communities). The remit of each normative organization is a particularly relevant determinant of the fragmentation of the human genome editing regulatory landscape given the number and variety of such organizations, which have been active in this field.

Second, the objectives that explain the normative actions are also a determinant of the fragmented human genome editing regulatory landscape as long as research, economics, public health, or bioethics objectives, for instance, are often the objects of different legal texts or at least of different rules within one legal text.

The third determinant of the fragmented human genome editing regulatory landscape relies on the various stages of development of therapy based on human genome editing techniques. Indeed, as observed in particular regarding substantive fragmentation, legal frameworks or normative recommendations target, for instance, the funding of research, clinical trials, patentability, or the marketing of medicinal products based on human genome editing techniques.

Fourth, regulatory fragmentation occurs according to the sources of human biological elements in which genome editing is conducted. Indeed, we have seen that different laws, rules, or recommendations apply to human genome editing on somatic cells and on embryonic or germ cells.

[88]http://www.academie-medecine.fr/wp-content/uploads/2016/02/Rapport-modification-du-g%C3%A8nome-27-01-16.pdf.

[89]See in addition to the National Ethics Committee that will be presented in this article, the joint communication from the INSERM Ethics Committee and the CNRS Ethics Committee on the Modification of the human germline genome by CRISPR. Serious ethical questions and condemnation following the announcement of the birth in China of genetically twins in China, December 2018; INSERM Ethics Committee Note of the Ethics Committee on the referral concerning issues related to the development of CRISPR-Cas9 technology February 2016.

[90]National Ethics Committee in France (Comité Consultatif National d'Ethique) opinion n°133 on "Ethical challenges of gene editing: between hope and caution" (2019).

[91]See *Discussion*.

[92]https://www.arrige.org/(last accessed October 2021).

Finally, the targeted population is also a determinant of the fragmented human genome editing regulatory landscape as long as the laws and the rules differ when the human genome editing techniques are to be conducted in the laboratory only for fundamental research, on clinical trials' participants, on an individual, or on numerous patients for therapy.

These determinants are very much interdependent as they often appear together in one regulatory text, although they generally imply different rules. They are part of the regulatory strategies to respond to human genome editing techniques, and as such, they contribute to the fragmentation process in order to adapt to the changing political and legal contexts. On the one hand, the process of fragmentation provides complementary rules to cover the entire field of human genome editing, such rules allowing a level of regulation (legal or normative, binding, or nonbinding) to be adapted according to territorial, institutional, or substantive aspects regarding legal, ethical, and societal implications. On the other hand, different rules from different organizations with various authoritative weights (e.g., binding or not) and the applicability of one or of several of these rules also raise legal challenges linked to potential overlapping and contradictions. Consequently, one could wonder whether the EU level or the national level of governance is the right place to pursue the regulation of human genome editing. The question may be unsolvable as both levels of governance have their own limits: the competencies limitations of the EU are salient given the cross-objectives linked to human genome editing, as well as the territorial limitations of each Member State regarding the movements across borders of persons, services, and goods including human genome editing techniques. On the opposite, the fragmentation process of the regulatory landscape allows to consider and balance various societal objectives, such as protection of fundamental rights and ethical values, protection of health, and access to safe innovative treatments, freedom of research, and competitiveness within the regulation of human genome editing. National laws and international regulations (including EU law), as well as various normative actors, are reflecting accepted social values regarding emerging technologies. Even if they are variations from one country or territory to another, the same goal is assumed in trying to balance between development and progress of science and protection of humans. While legal frameworks, such as human rights, are challenged especially regarding the emergence of human genome editing technologies (van Beers, 2020), "genome editing products could be seen as a test case for estimating the impact of legislative and nonlegislative actions, as well as investments by the EU and also as a measurement of the competences and capacity of the regulatory system."[93] In that sense, we have argued that fragmentation of the law as a dynamic process provides room for current and future solutions for more contingent responses to human genome editing reflecting the changing political, legal, and social contexts.

Nevertheless, it may be too reductive to think the regulatory landscape of human genome editing is solely fragmented as several normative activities show a tendency to provide common rules or rules as a set. For instance, the Joint Statement of Ethics Councils from France, Germany, and the United Kingdom on the Ethics of Human Heritable Genome Editing[94] follows the national positions previously adopted by these three committees in this regard[95] and provides common recommendations. It particularly shows that, despite different bioethical backgrounds, a consensus should be reached, although what is meant by "consensus" as well as how we will know it will be achieved should be clarified (Morrison and de Saille, 2019). As an introduction, the three committees recognized that their national positions were based on the core bioethical principles inherited from Beauchamp and Childress (2001) but differently balanced according to the national context and theoretical grounding. While solidarity and social justice were at the heart of the Nuffield Council of Bioethics opinion, beneficence and nonmaleficence founded one of the French and of the German ethics committees. The latter, the Deutscher Ethikrat, also built its opinion on human dignity, protection of life and its integrity, freedom, naturalness, and responsibility. Nevertheless, the three committees moved forward and assumed together that they "can conceive of cases where the clinical application of heritable genome editing could be morally permissible. We do not, therefore, consider the human germline categorically inviolable."[96] However, the councils differ on how this permissibility should be implemented and where should the limits be set.[97] As long as the core biomedical principles (beneficence, nonmaleficence, autonomy, and justice) are no longer considered as an absolute limit to use germline genome editing, and the National Councils have open room for discussions for its use in the medical interest of patients or their offspring, this position, even though not binding, could influence further revisions of the French Bioethics Law or of EU law in the future. Another example is the imaginary built into the framing of EU level legal regulation of human gene editing technologies, which is based on the tension around naturalness; safeguarding morality and ethics; and the pursuit of medical objectives for the protection of human health (Mahalatchimy et al., 2021).

[93]European Medicines Agency and Heads of Medicines Agencies. Genome editing EU-IN Horizon Scanning Report, *op. cit*. p. 10

[94]Nuffield Council on Bioethics, Deutscher Ethikrat, Comité Consultatif National d'Ethique, Joint statement on the Ethics of Human Heritable Genome Editing, March 3, 2020: https://www.ccne-ethique.fr/sites/default/files/press_release_-_heritable_genome_editing_def.pdf.

[95]Comité Consultatif National d'Éthique, Deutscher Ethikrat and Nuffield Council on Bioethics, Joint statement on the ethics of human germline interventions, March 3, 2020. https://www.ethikrat.org/fileadmin/Publikationen/Ad-hoc-Empfehlungen/englisch/joint-statement-on-the-ethics-of-heritable-human-genome-editing.pdf (last accessed June 18, 2021).

[96]Joint Statement *op. cit*.

[97]"Whilst all three reports offer reasons to conclude that the use of heritable genome editing could be acceptable to prevent the intergenerational transmission of serious hereditary disorders, the CCNE expresses a complete ethical opposition to 'enhancement' applications. The Deutscher Ethikratrecommends that the assessment of such applications should be made on a case-by-case basis. The Nuffield Council does not advocate distinguishing acceptable and unacceptable uses on a categorical basis but recognizes that judgments must take into account the interests and responsibilities of those affected in a given sociotechnical context." Joint Statement *op. cit*.

These examples highlight the defragmentation, understood as gathering together or connecting at least in some areas, may also be another characteristic of the human genome editing regulatory landscape. Therefore, both fragmentation and defragmentation may be a relevant grid of analysis to further decipher the regulatory landscape of human genome editing. Although it would require distinct research, which is not covered in this article, the French National Agency for Research–funded project I-BioLex on "fragmentation and defragmentation of the law on biomedical innovations," going beyond human genome editing, is conducting such analysis from 2021 to 2024.[98]

AUTHOR CONTRIBUTIONS

AM and ER-S contributed equally to the conception, research and writing of this article. AM has worked more on the EU level regulatory landscape and ER-S more on the French level regulatory landscape. All authors contributed to manuscript revision, read, and approved the submitted version.

FUNDING

This work has been supported by ANR-funded I-BioLex project (ANR-20-CE26-0007-01, coord. AM) and by ANR-funded project ComInGen (ANR-18-CE38-0007, coord. V. Tournay).

ACKNOWLEDGMENTS

The authors deeply thank Eloïse Gennet for her careful review of the English language.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Political Science

PERSPECTIVE
published: 25 February 2022
doi: 10.3389/fpos.2022.825496

Contiguous Governance of Synchronic and Diachronic Changes for the Use of Genome Editing Technologies

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Genome editing technologies are increasingly coming under scrutiny, based on various social value judgments in biomedical research, clinical care, and public health. A central cause of this sociotechnical tension is that these technologies are capable of precisely and easily creating genome-modified organisms and human cells and tissues. To exemplify a general framework for a national governance system of genome editing technologies, we first look at the regulatory dynamics in Japan. Second, we expose the potential tension between national and international debates and directions for the global harmonization of genome editing technologies. Third, underpinning these two perspectives, we propose *contiguous governance* as a novel model of the governance of emerging biotechnologies from both synchronic and diachronic perspectives. These perspectives, derived from genome editing technologies, can contribute to a better understanding and consideration of future regulations and governance systems.

Keywords: governance, syncronicity, diachronicity, genome editing, future generations

OPEN ACCESS

Edited by:
Alberto Asquer, SOAS University of London, United Kingdom

Reviewed by:
Florian Rabitz, Kaunas University of Technology, Lithuania

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

Received: *30 November 2021*
Accepted: *01 February 2022*
Published: *25 February 2022*

Citation:
Minari J, Shinomiya N, Takashima K and Yoshizawa G (2022) Contiguous Governance of Synchronic and Diachronic Changes for the Use of Genome Editing Technologies. Front. Polit. Sci. 4:825496. doi: 10.3389/fpos.2022.825496

INTRODUCTION

Compared to conventional methods, current genome editing technologies enable handy and precise genetic control over a broad range of organisms and human cells. While this new power is a boon to medical research, clinical care, public health, and the economy, using these technologies can also lead to various ethical, legal, social, and policy tensions. In particular, their uncertain and possibly irreversible influence on not only present generations but also future generations has prompted investigations into proper regulations and governance systems. Many international institutions and organizations are addressing these emerging challenges. For instance, the World Health Organization (WHO) has significantly contributed to the creation of key documents aimed at managing human genome editing and genetically modified mosquitoes (World Health Organization, 2021a,b,c). This international approach is effective in encouraging scientific development and assessing its ethical and social impacts such that key stakeholders in many countries can reach a consensus on the development of related governance systems. To revisit and foster the harmonization of related regulatory and governance systems, we first explore a case study of the impacts of Japanese regulations on genome editing technologies in biomedical fields. We then consider potential challenges in the development of a global governance framework. Ultimately, we suggest a *contiguous governance* model that focuses on the synchronic

and diachronic aspects of using emerging biotechnologies. Here, the synchronic aspects represent national and international regulations and governance systems over a limited time span, which can be interpreted as a way to highlight the spatiality of governance at a particular time. On the other hand, the diachronic aspects reflect time-course regulations and governance systems bridging the past, present, and future. Instead of individually addressing the current challenges in regulations and governance, we discuss three major initiatives for implementing contiguous governance to spur further fundamental debates and measures in the management of emerging biotechnologies.

PART 1: JAPANESE REGULATION OF GENOME EDITING TECHNOLOGIES

In Japan, the emergence of genome editing technologies has resulted in three key regulatory impacts in the biomedical field. The first concerns the interpretation of the *Japanese Cartagena Act* (formally, the *Act on the Conservation and Sustainable Use of Biological Diversity through Regulations on the Use of Living Modified Organisms)*, which was enacted in 2003 to observe the *Cartagena Protocol on Biosafety to the Convention on Biological Diversity*. This act is deeply associated with research, care, and public health, as it governs the use and related biosafety issues of living modified organisms (LMOs). In fact, the Japanese government recently ruled that genome-edited end products should be classified as LMOs unless they have "no remnants of inserted nucleic acid or its replicated product" (Tsuda et al., 2019).

The second impact concerns the handling of somatic genome editing for clinical applications, which is associated with three key regulatory considerations. The regulatory considerations for the marketing authorization and approval of genome editing products have already been addressed by the Science Board of the Pharmaceuticals and Medical Devices Agency of Japan (Yamaguchi et al., 2020). Moreover, the *Act on the Safety of Regenerative Medicine*, which regulates *ex vivo* genome editing for clinical research and care, was partially revised in 2020 to reclassify the use of gene-edited cells as a high-risk category, as these cells are relatively novel, along with induced pluripotent and embryonic stem cells (Takashima et al., 2021). Furthermore, the *Guidelines for Gene Therapy Clinical Research*, which cover *in vivo* genome editing for clinical research (but not for clinical care), were amended in 2019 (Uchida, 2020) to redefine their scope and definition (e.g., to include genome editing without gene transfer) and to align them with the *Clinical Trials Act*. It should be noted that these non-legally binding guidelines prohibit germline genome editing for clinical applications. Attempts are underway to bridge the gap between the regulatory pathways of *ex vivo* and *in vivo* genome editing (Takashima et al., 2021).

The third impact is related to the nature of human germline genome editing for basic research. In 2019, the *Guidelines for Research Using Gene-Altering Technologies on Human Fertilized Embryos,* were established. While these guidelines originally regulated studies that used genome editing for assisted reproductive technology (ART), their 2021 revision also allowed for research with genome editing for hereditary or congenital diseases. Another set of guidelines, *Ethical Guidelines for Assisted Reproductive Technology Studies Involving Production of Human Fertilized Embryos,* included the use of genome editing technologies through a 2021 revision. This indicates that research using genome editing for the production of human fertilized embryos for ART is allowed. Furthermore, governmental papers suggest that these guidelines are likely to be revised to allow for research with genome editing for hereditary or congenital diseases. While various debates have arisen on the handling of human embryos (Nakazawa et al., 2018), these regulations have paved the way for applying genome editing for human embryos, albeit with limited purposes and relevant conditions.

These impacts show that, even with rapid and proactive regulatory responses to genome editing technologies in Japan, three challenges remain in improving the current regulatory system. First, there is no comprehensive perspective on the regulation of genome editing. In other words, to date, regulatory attention has been limited to their specific and segmented elements: LMOs, somatic and germline genome editing, basic research and clinical applications, *ex vivo* and *in vivo* genome editing (somatic genome editing for clinical applications), and pre- and post-embryo editing (germline genome editing for basic research). Second, there are many overlapping regulations. For example, *in vivo* somatic genome editing (clinical research) can be governed by three different regulations: *Guidelines for Gene Therapy Clinical Research*, *Clinical Trials Act*, and *Japanese Cartagena Act*. Third, the coverage/scope and forms (i.e., legally binding or non-legally binding) of the regulations are not yet optimized in the context of biomedical research and clinical care.

While these challenges likely arose due to the conventional approach to formulating specific regulations in response to the emergence of new technologies, the continuous emergence of new technologies can necessitate more regulatory efforts. This can result in an administrative burden and a maze of regulations (Minari et al., 2021). In this scenario, while *ad-hoc* regulations are important short-term solutions, fundamental regulations must be established over time. Moreover, we must constantly re-evaluate the fundamental regulations in light of the new *ad-hoc* regulations introduced over time to ensure they remain relevant. At the same time, *ad-hoc* regulations must be framed on the same principles as fundamental ones; in essence, both regulation types must be compatible with each other. In the case of genome editing, these initiatives should include a comprehensive consideration and review of relevant fundamental elements, that is, of the implications of genetic editing, the handling of organisms and human cells, the significance of biosafety, potential limitations for basic research, and the social meaning of unproven therapies. This integrative perspective can contribute to the formation of systematic and robust regulations and governance systems.

PART 2: CHALLENGES FOR THE GLOBAL GOVERNANCE OF GENOME EDITING TECHNOLOGIES

The notion of governance, with its references to power, actor networks, and decentralization, comes from modern social and institutional settings, which have reached a global scale. Despite the ambiguous and variable nature of global governance, it has increasingly become the focus of attention as an approach to dealing with the complexities of a dynamic, interactive, and international society and developing specific and feasible solutions for sociotechnical issues. However, given the robust interoperability of genome editing technologies, the absence of clear global laws poses a potential challenge for implementing global governance. While a nation can control and adjust its specific regulations to some degree, no single authority can manage global regulations and governance. Although having such an authority would entail various advantages and disadvantages, reflecting on the nature of the current international governance system can provide a better solution.

In the current governance structure, at least three key approaches can be identified for developing mutual trust and shared responsibility between states. The first approach is to conclude international conventions, such as the *Oviedo Convention* and the *Convention on Biological Diversity*. The second is to issue recommendations and guidelines through representative international organizations, such as the WHO, the United Nations Educational, Scientific, and Cultural Organization (UNESCO), and the Organization for Economic Co-operation and Development (OECD). For instance, the WHO highlighted the importance of better global governance and called for a monitoring system with a human genome editing registry (World Health Organization, 2021a,b). The third approach is to shape the statements and reports of national academies or independent organizations on bioethics and academic communities (Marchant, 2021). These approaches are vital to the formation of an international framework beyond national boundaries and the rapid integration of expert knowledge from different angles. However, they do not necessarily ensure effective global governance.

The limitations of the current governance structure include its non-conforming, gradual, and asymmetric elements. First, international conventions can provide a common stable regulatory and normative space for robust action, but they inherently create loopholes for non-member states and global corporations. Moreover, consensus among several actors is not always achievable; thus, it is not surprising that, in an international context, regulations on germline genome editing for clinical applications are inconsistent and have differing degrees of control (Araki and Ishii, 2014). Second, while international organizations and institutions provide some degree of professional consensus, they not only have an indirect influence on the regulatory initiatives of individual states but also tend to adopt stepwise measures in response to the progress of science and technology. These can be regarded as deliberate approaches to the gradual expansion of genome editing technology use without prior restrictions and prohibitions. Finally, there can be an asymmetric relationship between relevant actors in terms of whether and how genome editing technologies should be handled. For instance, as a premise, some major actors are keen on the broad and rapid use of such new technologies rather than conventional and alternative ones.

In fact, the current global governance of genome editing technologies aims to establish a common, well-defined framework for a harmonious mindset and shared understanding without adopting strong international initiatives, as in the case of human cloning. However, given the current decentralized governance system, global and synchronic prohibited issues related to genome editing technologies are not regulated in a clear or unified manner. From a governance perspective, even minimal levels of prohibition should be universally identified, shared, and agreed upon. In this sense, a promising governance system would be neither centralized nor decentralized, but polycentric, involving a broad range of stakeholders, such as players, intermediaries, regulatory agencies, and/or funders. Such a system would also be tolerant of divergent and ambiguous values and views aimed at "opening up" governance commitments on these technologies (Stirling, 2008). This governance perspective can also be employed to adjust relationships between science and technology policies, public funding and market mechanisms, and ethico-legal regulations.

Viewed through the lens of genome-editing technologies, the governance of emerging biotechnologies *over time* has two potential challenges. The first is closing the growing gap between the emergence and accelerating application of technology and traditional regulatory action timelines (Bennett Moses, 2007; Marchant, 2011). One practical approach to this pacing problem is a technological slowdown (Linstone, 1996; Woodhouse, 2016). Yet, moratoriums—an oft-used tactic for sensibly suspending scientific development by leaving the future open and taking time to consider the optimal decision (Chesneaux, 2000)—may not necessarily be a viable measure and may be criticized as empty gestures or pure public relations, as was the case of dual-use research on the H5N1 bird flu (Malakoff, 2012; Engel-Glatter, 2014). Moratoriums may even be rejected outright by technology-friendly countries for gene drives (Callaway, 2018). The other approach is regulatory speedup. This has already emerged in the modern governance context, as national and international stakeholders, who are generally impatient by nature, demand immediate action, rapid conformity, fast concordance of norms, and short-term convergence of practices (Halliday, 2017). In addition, national governments generally tend to concentrate on topical problems over future ones (Hoogerwerf, 1990). However, such fast policy solutions may increasingly disrupt and obliterate long-term decision-making cycles, institutional memory, and efforts to anticipate future difficulties and policy failures (Jessop, 2002). To extend beyond the two approaches of "technological slowdown" and "regulatory

speedup" described above, a possible remedy is to cautiously set minimum levels of restrictions and limit the scope of application of the technology and appropriately revise or redefine this scope through continuous monitoring and intervention. In other words, social applications of the technology must be carefully promoted, while the minimum restrictions are identified and maintained.

The second challenge is to reconcile or accommodate different time perceptions to shape future visions and perspectives based on cultural backgrounds and psychological presuppositions (Das, 1991; Hofstede, 1993; Meyer-Sahling, 2007). The subjective recognition of time has non-uniform and elastic characteristics and leads to differing visions for the future. For instance, a Japanese public survey on genome editing technologies has shown that the adoption of different scopes and ranges of the future is deeply associated with different (often ambiguous) decisions and attitudes toward such technologies (Hibino et al., 2019). Similarly, a policy study on synthetic biology has demonstrated that even analytical future-oriented discourses are socioculturally and institutionally bounded, and options for present and future generations remain limited (Yoshizawa, 2019). Notably, the future is often discounted by the subjectivity, ambiguity, and contextuality of time perceptions.

DISCUSSION: THREE INITIATIVES FOR CONTIGUOUS GOVERNANCE

Traditional approaches to managing genome editing technologies are primarily synchronic and spatial in scope. Thus, the lack of diachronic perspectives on regulations and governance is increasing. This article diverges from academic debates centered on discourse and rhetoric and demands more fundamental and viable action to improve future regulations and governance systems for emerging biotechnologies. We propose a contiguous governance approach that focuses on both geopolitical landscape and diachronic perspectives. This approach comprises three complementary initiatives: improvement of historical literacy, empowerment of future generations, and development of a sustainable material culture.

When scientific progress is closely related to economic growth, high stakes gradually undermine the precautionary approach to the development and use of emerging biotechnologies. However, memorable events can always bring us back to our ethical basics. Our first proposed initiative is the improvement of historical literacy, that is, remembering and reinterpreting some watershed events or historical tipping points. These tipping points include the Asilomar Conference on Recombinant DNA in the U.S., the first baby born through *in vitro* fertilization in the UK, and the first babies born with edited genomes in China. Promoting and developing historical literacy illuminates ways to offer a softer and less direct form of regulatory coordination than with substantive law. Such coordination may then provide a firm legal foundation for co-regulation, or "regulated self-regulation," as hybrids between state regulation and self-regulation, through institutionalized legal procedures and organizational norms (Scheuerman, 2001). It also leaves a regulatory margin for future responses to temporal changes by accepting systematic and functional redundancy in any governance.

While people exhibit differences in their perceptions of time and tend to discount the future in favor of the present, our second proposed initiative is the empowerment of future generations who are keener to face and tackle the planetary crisis than incumbents. Due to their longer life expectancy, young people can become more far-sighted and responsible. Besides the necessity of providing civic youth science engagement projects (Mayhew and Hall, 2012; King et al., 2021), a direct and plausible political action would be to lower the voting age (Leece, 2009) or introduce a new voting system in which parents are allowed to vote as proxies for their children (Demeny, 1986). A more feasible and softer solution may include establishing a training grant program for the youth to enable them to gain scientific knowledge, learn its social implications, and have a more articulate voice in policymaking and social decision making.

Our third proposed initiative is based on a more ontological and longer-term perspective: the establishment of sociotechnical objects or materials and related public spaces for remembering, reflecting on, and connecting the dynamics of norms from the past, present, and future. It makes little sense for an object or material to simply exist in which human norms and values are embedded in some design approaches, such as "value sensitive design" (Friedman and Hendry, 2019) and "ethics by design" (Dignum et al., 2018). This is because it deprives us of opportunities to regularly review what is ethical in the interaction between humans and objects. Such design approaches also entail the risk of inviting technological fixes. Some recent examples of technological fixes are restricted gene drives (Noble et al., 2019; Bier, 2022) and genetically engineered apples that never turn brown (Maxmen, 2017), which may be durable and environmentally friendly but are less respectful of natural products and processes. In addition, our relentless pursuit of convenience through objects and organisms must be questioned. Such an engineer- or user-oriented solutionist approach is shortsighted and suboptimal and lacks functional redundancy and dynamic capabilities for sociotechnical change.

An alternative idea is the development of a sustainable material culture. The Future Library is a public artwork project in which a forest was planted in Norway to supply the paper for a special anthology of books to be printed in 100 years. The forest's existence is subject to whatever has happened to the environment over that century (Paterson, 2014; Mickiewicz, 2016). A similar but more sustainable project is the millennium-long ritual of rebuilding and renewing a Japanese Shinto shrine every 20 years to maintain a sacred place and foster technical skills as "everlasting youth" by cultivating timber and human resources across the country (Lopes, 2007). Similarly, the governance of genome editing technologies and other emerging biotechnologies must be based on a culture of continuous human intervention in

society through which the ecological and social resources and systems necessary for the technologies become more sustainable. This requires continual awareness that governance policies must be geopolitically and diachronically contiguous. All of this depends on how we envisage the kinds of apples we will need in the distant future and in what environments.

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/s.

AUTHOR CONTRIBUTIONS

JM and GY conceived and drafted the study. NS and KT revised the manuscript. All authors made key contributions to the development of the final manuscript and approved its publication.

FUNDING

This research was partly supported by the SECOM Science and Technology Foundation and by the JSPS Grant-in-Aid for Scientific Research (B) (21H03163). JM is also partly supported by the JSPS Grant-in-Aid for Challenging Research (Pioneering) (20K20493).

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Political Science

ORIGINAL RESEARCH
published: 24 March 2022
doi: 10.3389/fpos.2022.800211

A Doomed Technology? On Gene Editing in Bavarian Livestock Agriculture, Policy Field Conflicts and Responsible Research and Innovation

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OPEN ACCESS

Edited by:
Michael Morrison, University of Oxford, United Kingdom

Reviewed by:
Pim Klaassen, VU Amsterdam, Netherlands
Jonathan Hankins, Fondazione Giannino Bassetti, Italy

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

Received: *22 October 2021*
Accepted: *19 January 2022*
Published: *24 March 2022*

Citation:
Müller R, Feiler J and Clare A (2022) A Doomed Technology? On Gene Editing in Bavarian Livestock Agriculture, Policy Field Conflicts and Responsible Research and Innovation. Front. Polit. Sci. 4:800211. doi: 10.3389/fpos.2022.800211

The emergence of CRISPR-Cas9 has recently, for the first time, rendered the large-scale genetic modification of livestock animals such as cows, pigs, and chickens possible. Novel editing targets range from genes that curb disease vulnerabilities, increase muscle mass, or convey hornlessness, to the development of transgenic pigs for medical use. In this article, we discuss the efforts of a transdisciplinary research consortium in Bavaria, Germany, to test the technical and social feasibility of using CRISPR-Cas9-based gene editing as a novel technology in Bavarian small- to medium-scale livestock agriculture. The consortium comprised life scientists, local breeding associations, legal scholars, and social scientists from Science & Technology Studies (STS) and aimed to promote Responsible Research and Innovation (RRI) for gene editing technologies. Research focused on gene editing applications that improved animal health and all editing targets were co-developed with local breeding associations to meet the situated needs of small- to medium-scale livestock farmers in Bavaria. In this article, we discuss why the agricultural stakeholders in the project, that is, the representatives of local breeding associations, considered that, despite the project's success in generating positive research outcomes, it would be unlikely that results will be implemented in Bavarian livestock agriculture. We describe this situation in terms of a tension between agendas in the science and technology policy field and in the agricultural policy field in Bavaria that impacts local farmers' ability to adopt gene editing technologies. We further discuss what it might mean for RRI practices if public stakeholders are unlikely to benefit from the outcomes of RRI practices due to policy field conflicts or other contextual constraints and how STS scholars and other social scientists involved in RRI projects could adjust their practices to possibly redistribute benefits.

Keywords: science and technology studies, agriculture, gene editing (CRISPR-Cas9), responsible research and innovation, policy field, Bavaria, Germany, livestock

INTRODUCTION

The emergence of CRISPR-Cas9 has recently, for the first time, rendered the large-scale genetic modification of livestock animals such as cows, pigs, and chickens possible (Lamas-Toranzo et al., 2017; Shriver and McConnachie, 2018). Prior techniques of genetic modification were effective on plants and smaller mammals such as laboratory mice; however, they were difficult to use in the larger mammals and birds typically found in livestock agriculture (Perisse et al., 2021). With the advent of CRISPR-Cas9, this has changed dramatically. While numerous questions still remain open, markedly the question of off-target effects (c.f. Middelveld and Macnaghten, 2021), CRISPR-Cas9 presents, for the first time, a technology that might allow scientists and breeders to engage in the large-scale genetic modification of agricultural livestock animals.

Historically, public debates about gene editing were largely focused on the genetic modification of agricultural plants and on biomedical applications. Only more recently, the genetic editing of livestock has become a topic of public discussion. While there has been some attention to the topic in mainstream media (see, e.g., WIRED, 2019 or New York Times, 2015), debates have significantly increased in the agricultural community and its public fora. Internationally, breeders have discussed gene editing with CRISPR-Cas9 as a new opportunity to accelerate and ensure success in breeding, particularly when it comes to breeding targets such as curbing disease vulnerabilities, increasing muscle mass or milk yields, or conveying other desirable traits, such as hornlessness in cows (Proudfoot et al., 2019; Yunes et al., 2019).

In this article, we discuss results from a research project that took shape amid these emergent debates. The project "FORTiGe – Forschungsverbund Tiergesundheit durch Genomik" (2018–2021) brought together a transdisciplinary research consortium in Bavaria, Germany, to test the technical and social feasibility of using CRISPR-Cas9-based gene editing as a novel technology in Bavarian livestock agriculture. The consortium was comprised of life scientists, legal scholars, and social scientists from the field of Science and Technology Studies (STS).

Importantly, the project focused on exploring the possibility of using CRISPR-Cas9-based gene editing in the context of, and for use in, small- to medium-scale, local Bavarian livestock agriculture. This is why the consortium also included local breeding associations who co-developed the targets for editing together with the scientists. That is, editing targets were selected based on the needs of local farmers in livestock agriculture in Bavaria. The consortium thus focused exclusively on targets that would improve animal health, specifically focusing on disease resistances. Animal health is an important concern for small- and medium-scale farmers, who often lack the economic resources to bounce back from a disease outbreak in their herds. Concurrently, focusing on animal health allowed the consortium to take a specific stance in a German context that is historically characterized by a very negative public reception and strict regulation of genetic technologies in agriculture. This negative public opinion is not least due to a perception that genetic technologies mainly benefit large-scale agricultural corporation by increasing their yields and profits and have no benefits for local farmers (Levidow and Boschert, 2011). The consortium aimed to break this perception by focusing on animal health and local farmers' needs instead of yields and collaborations with larger corporations.

This specific research design successfully convinced a major Bavarian research funder to fund this project though they knew it would be a controversial topic. In recent years, Bavaria has made a distinct effort to cast itself as a high-tech state, investing significantly in research and innovation in Bavaria (High Tech Agenda Bayern, 2019). Concurrently and interestingly, Bavaria has also increased funding for interdisciplinary work that explores the social, political, and ethical aspects of emerging technologies, for example, through dedicated research institutes (see, e.g., the Bavarian Research Institute for Digital Transformation)[1] and strategic reorientations at some of its major universities (see, e.g. the TUM Agenda 2030)[2] toward "Responsible Research and Innovation" (RRI). RRI is both a research approach and a policy framework that proposes a multi-stakeholder approach toward innovation that is based on the principles of anticipation, inclusion, reflexivity and responsiveness (Stilgoe et al., 2013). Possible technology users and others affected by a potential innovation should be included in the innovation process in order to anticipate and reflect on its wider social, economic or political impacts and in order to responsively adjust research and innovation processes to avoid harm and increase benefits for society and public stakeholders. As Bavaria increasingly subscribes to an RRI framework as a preferred path for fostering innovation, funding a project on gene editing as an important emergent technology that is inter-and transdisciplinary in nature and promotes RRI is, hence, clearly in line with Bavaria's current science and technology policy profile.

However, in this article, we will examine what happens if the orientations and incentives put forward by science and technology policy are at odds with those of another policy field that is of equal or, in fact, greater relevance for the public actors involved in an RRI project. We will sketch how the incentives to promote gene editing in Bavaria in a transdisciplinary manner clash with the perceived incentives put forward by the agricultural policy field—incentives that significantly circumscribe the possibilities of practice of the agricultural partners in the project. Following critical research that explores the limitations and possibilities of putting RRI principles into practice in situated contexts (e.g., de Hoop et al., 2016; Macnaghten et al., 2022), we will analyze this conflict and discuss what these tensions imply for the possibility of practicing RRI "responsibly" in the field of gene editing in livestock agriculture in Bavaria and possibly in other fields of research, too.

INCENTIVE CONFLICTS IN CONTEMPORARY AGRICULTURE

Agriculture is a contested field of human activity today. While without a doubt, human survival is dependent on agricultural

[1]https://www.bidt.digital/en/

[2]https://www.exzellenz.tum.de/en/exzellenz/university-of-excellence/

harvest, practices in agriculture have been criticized for their impact on the environment, their treatment of animals, and their contribution to climate change (Feola et al., 2015; Baur, 2020). This has led to increased attention to agriculture from policymakers, resulting in stricter regulations for animal welfare and environmental protection (Schmid and Kilchsperger, 2010; Vogeler, 2018) in some national contexts such as Germany and increased attention from researchers who aim to optimize agricultural practices through scientific and technological innovations. Meanwhile, market actors, such as large-scale retailers and supermarket chains, have also begun to respond to public debates about agricultural practices by introducing product lines and labels that offer agricultural products to consumers which adhere to stricter environmental and animal welfare standards (Vogeler, 2019). These are just some examples of current dynamics that showcase the complexities of agriculture as a policy field. Our understanding of "policy field" here follows a Bourdieuian conceptualization of social fields (Bourdieu and Wacquant, 1992; Fligstein and McAdam, 2012): we frame policy fields as social arenas where both state and non-state actors interact, collaborate, and struggle with each other in practices of meaning-making (c.f. Pohle et al., 2016).

However, in this article, we are not focusing on analyzing the specific make-up and dynamics of this policy field in Bavaria. This beyond the scope and the data of the project at hand. Rather, we are interested in understanding how agricultural stakeholders—in our case, representatives of local Bavarian livestock breeding associations—understand the complexities of this policy field from their situated perspective and how they interpret its incentives. We further aim to understand how they articulate these incentives together or in tension with incentives and opportunities formulated by science and technology policy, available and relevant to them through long-standing ties and collaborations with local life science researchers and their involvement in the RRI-oriented research project at hand.

With our analysis, we first aim to contribute to the recently growing literature around incentive conflicts in agriculture, particularly with regard to "right vs. right" conflicts. Baur (2020) elucidates the problem of incentive conflicts in agriculture by discussing how farmers in California have responded to concurrent calls to increase the food safety of their products and to develop more sustainable and climate-friendly practices—both calls that many farmers find important and agree with in terms of their personal value-orientations. Baur shows that a majority of farmers, however, opt for increasing food safety rather than focusing on climate-friendly farming practices because increasing food safety is "perceive[d] as most feasible within the bounds imposed by their institutional environment and [. . .] aligns more consistently with multiple institutional drivers than does environmental sustainability. While food safety finds broad support in comprehensive rules, standards, and market mechanisms, sustainability is often implicitly discouraged by market mechanisms and receives only disjointed support from fragmentary rules and standards." (Baur, 2020, p. 1185).

Baur here shows that choices in agriculture are poorly understood through a pure analysis of value orientations or preferences. He suggests instead "that each choice belongs to complete, but divergent, institutional logics, each with its own set of constitutive institutional carriers" (Baur, 2020, p.1178) and must be understood and analyzed as such. Importantly, drawing on Feola et al.'s work (Feola et al., 2015), he argues that farmers tend to comply in particular with incentives put forward "by powerful social actors whom they believe are beyond their ability to influence" (Feola et al., 2015)—such as, in the case of food safety, retail and supermarket chains who dictate strict food safety rules and hold farmers accountable for outbreaks. This analysis of how constrained choice emerges holds particularly true for small and medium-scale farmers, who often have less wiggle room to respond to multiple calls to action at once than larger businesses and have to choose carefully where they invest their resources.

We will show that, in our case, similar tensions between diverging incentives and diverging visions for the future of agriculture in Bavaria and the possible role of genetic technologies within it are at work. Each vision is advocated for by a different actor constellation, whose ability to shape the future has to be assessed by farmers, breeders, and their representatives in order to forge their own path forward. Part of this complex field of tension is a misalignment of science and technology policies and agricultural policies in the Bavarian context, which we will explore in our empirical analysis. We will argue that careful attention to these tensions between incentives from different policy fields is important for RRI practitioners who aim to practice RRI responsibly as these tensions can significantly circumscribe the possibility for public stakeholders, such as in our case the agricultural stakeholders from local breeding associations, to benefit from RRI projects. We will discuss possible implications for RRI practices, particularly, how STS scholars and other social scientists involved in RRI might be able to respond to such challenging situations, which is where we locate the second key contribution of this paper to the current literature.

MATERIALS AND METHODS

For our analysis, we draw on a range of materials which we collected as embedded social scientists in the FORTiGe project (2018–2021). As discussed above, the FORTiGe project was conducted by a transdisciplinary research consortium consisting of life scientists, legal scholars, and social scientists from the field of Science & Technology Studies (STS) as well as representatives of local breeding associations. The project focused on exploring the possibility of using CRISPR-Cas9-based gene editing for use in small- to medium-scale, local Bavarian livestock agriculture and focused exclusively on targets that would improve animal health by mediating disease resistances.

Our STS project component aimed to explore the perspectives of two different publics on gene editing in Bavarian livestock agriculture: the wider Bavarian public and small- to medium-scale Bavarian farmers. As a basis for engaging these publics, we developed a range of scenarios based on gene editing applications that were considered possible and beneficial

by the life scientists and the representatives of local breeding associations. Project methods included:

- Semi-structured interviews with researchers and agricultural stakeholders in Bavaria within and beyond the project consortium
- Scenario-based focus groups with members of the lay public that discussed possibilities of using CRISPR-Cas9 for gene editing in Bavarian livestock agriculture
- Semi-structured interviews with Bavarian small- and medium-scale farmers about these possibilities
- Participant observations of project meetings and related public events
- A workshop where we presented results from the focus groups and the interviews with farmers to the project consortium, including the agricultural stakeholders, and discussed, in terms of RRI, what our results might mean for the socially responsible development of livestock gene editing in Bavaria

For this specific article, we draw upon all empirical materials that specifically engaged agricultural stakeholders in the project consortium, i.e., the representatives of local breeding and farming associations in Bavaria. These stakeholders are particularly aware of the dynamics in the agricultural policy field in Bavaria and frequently related and evaluated the project's goals within this context. These materials specifically include the semi-structured interviews with agricultural stakeholders in Bavaria who were project members and with some of their colleagues (seven persons), observations at project meetings over the course of 3 years as well as, importantly, the discussions of our results and future possibilities for livestock gene editing in Bavaria at our final project workshop. All interviews were recorded, transcribed, and informed consent was obtained before each interview. At project meetings, field notes were taken. The final workshop was recorded and transcribed for analysis, including break-out groups where researchers, agricultural stakeholders, social scientists, and legal scholars discussed the possible futures of livestock gene editing in Bavaria and what it could mean to develop and use this technology in a responsible manner. The topic of tensions between the efforts of the project and the agricultural policy landscape in Bavaria emerged as an important theme at this final workshop. It served as a sensitizing concept (Blumer, 1954) in the consequent grounded theory analysis (Charmaz, 2006) of all relevant materials. We performed multiple rounds of open and focused coding in the project team, which consisted of three team members, shared coding results to improve intercoder reliability, and discussed emergent themes and coder memos in order to allow the nascent results to inform the ongoing analysis. The results of this analysis are present in this article.

Below, we outline the results of this analysis. We draw particular attention to two moments in the project that showcased the tensions between the project's goals, funded and supported by key actors in the Bavarian science & technology policy field, and the agricultural stakeholders' perceptions of the agricultural policy field and their room to maneuver within it, tensions which had significant implications for the possible meanings of RRI in the project context. The first moment arose already during the formation of the consortium and contestations surrounding its design and funding; the second moment concerned the agricultural stakeholders' reception of and response to the results of the STS project component, i.e., the results of the focus groups with the lay public and the interviews with farmers.

A CONSORTIUM IS FORMED

In order to adequately contextualize the results of the FORTiGe project, it is important to start by discussing the tensions that surrounded its inception. The project was conceived by highly esteemed researchers at a renowned university in Bavaria. Having had a long and successful track record in animal biotechnology and livestock breeding, they recognized that CRISPR-Cas9 could be a game-changer, not only for their research, but also for developing real-world applications for livestock agriculture. The two most senior researchers of the group had both lived through the vehement rejection of genetic technologies for agricultural use, mainly plant breeding, in Germany in the 1990s and early 2000s. Because of these histories and what they perceived to be an unchanged public attitude toward green biotechnologies, both were concerned that CRISPR-Cas9 based gene editing of plants and livestock would, despite the novel technological approach, constitute a "doomed technology" in the German context.

Both researchers had a critical stance toward the role of researchers in prior debates about genetic technologies in Germany. Notably, one of the researchers often remarked that scientists should have taken a more active role, not only in discussing technical risks and technical safety, but also in addressing the social and political aspects of genetic technologies, e.g., by actively working to not only make technologies available for international agricultural conglomerates, but also develop use cases for smaller farmers or maybe even exclusively realigning their research agendas with the needs of smaller farmers.

The FORTiGe project was born out of the desire to learn whether, if such an approach was taken with CRISPR-Cas9, it could create new opportunities for genetic technologies in agriculture in Bavaria. The scientists thus reached out to local breeding organizations and like-minded researchers to form a transdisciplinary consortium. They decided the project would only address targets deemed important by local farmers and breeders, which led to the shared decision to focus exclusively on editing targets that improved animal health and not, for example, yields. For these specific targets, the researchers wanted to explore if editing was possible, i.e., if a disease resistance could be conveyed through genetic edits, and if it was possible without off-target effects or other negative impacts on the animals' health and well-being. The researchers also reached out to social scientists in STS (the authors of this paper) and legal scholars to join the consortium. The core idea of the project was to explore the technical, social, and legal feasibility of using CRISPR-Cas9 for livestock gene editing in Bavaria alongside and in conversation with each other.

The representatives of local breeding organizations were both highly interested in and skeptical of the project from the start. They knew that they themselves and many of the members of their associations were motivated to learn more about if and how novel genetic technologies could improve breeding outcomes. They were already using genetic analysis to select animals for breeding, and the prospect of utilizing gene editing to improve certain traits, particularly to reduce vulnerabilities to infectious diseases and hereditary defects—some of which had occurred due to the limitations of conventional breeding methods—was highly attractive to them.

It is important to note that while these stakeholders had a very practical background in agriculture, such as coming from farming families or having training in practical agronomy, many had also studied at the university and were familiar with the advances of agricultural science. Similarly, and possibly contrary to public perception, many livestock farmers are regularly in contact with genetic technologies, for example, because of the genetic analysis of their livestock. Working with CRISPR-Cas9 thus represented, for many, rather an extension of their engagement with genetic technologies than a *de novo* introduction.

However, despite their practical interest in the technology, representatives of breeding associations were, from the start, skeptical if there would ultimately be a place for livestock gene editing in Bavaria. This skepticism was rooted not so much in questions concerning a possible interest in their own breeding and farming community, but rather in the configurations of the wider policy field that shape their range of action. While we will analyze these constraints in more detail below, at the point of the project application, these concerns were simplistically framed as a problem of "public acceptance" of these new technologies—a problem that should be addressed by the social scientists on board (who, of course, immediately reframed the issue from one of unidirectional acceptance toward one of contestations over values, interests, and power structures).

Including social scientists in the project was part of the life scientists' credibility work within and beyond the consortium: having researchers on board who would engage the public and examine their perspectives on livestock gene editing was important for the agricultural stakeholders to agree to participate in the project and it was also regarded favorably by the funding agency. Similarly, both agricultural stakeholders and funders deemed it essential to have a legal scholar on board who would assess the legal feasibility of gene editing applications in a dynamic landscape of national and European legal regulations. Overall, by combining these different aspects in one project, the life scientists successfully promised to possibly develop a form of "thick legitimacy" (de Wit and Iles, 2016) for livestock gene editing in Bavaria by performing a number of "credibility tests" (de Wit and Iles, 2016) with regard to the scientific, social, and legal dimensions of using gene editing in Bavarian livestock agriculture. This argumentation convinced the funder, and they ultimately supported the project, despite the arguably controversial character of the project topic—after all, the two senior researchers in the project were not the only ones in the research and the policy community who considered that gene editing might be a "doomed technology" in the German context.

RESEARCH RESULTS AND RECEPTION OF RESULTS IN THE CONSORTIUM

After nearly three years of research, the consortium had gathered a range of results. Markedly, life scientists had successfully identified a range of targets to decrease specific disease vulnerabilities in cows, pigs, and chickens and had effectively conducted proof-of-concept experiments. While for some researchers some questions still remained open, for example concerning off-target-effects for some specific targets, overall, the group was confident that, if it were legally possible, they could start working with breeding organizations to cultivate genetically edited livestock in the near future. Legal analysis focused primarily on commenting on and offering alternative visions to the recent European Court of Justice verdict which ruled that organisms which have been edited with CRISPR-Cas9 GMOs must be regulated under the common European GMO law. Our social science analysis offered two sets of insights, which we presented to the consortium at an RRI-themed workshop in year three. These insights have been and will be published elsewhere (Müller et al., 2021; Clare et al., forthcoming; Feiler et al., forthcoming) and are summarized below in in order to set the stage for the subsequent discussion with the consortium members.

We first presented results from the focus groups with members of the Bavarian public (Clare et al., forthcoming). In the focus group, we had presented the participants with different scenarios of using gene editing in agricultural and biomedical contexts and, markedly, with scenarios that hat connect both contexts. For example, we discussed scenarios where genetically editing chickens could prevent the spread of the bird flu among chickens and thus eliminate the culling of thousands of chickens in Germany every year, as well as the spread of the bird flu from chickens to humans. While participants generally found this possibility interesting, most of them ultimately argued against it, as they considered bird flu outbreaks as the result of factory farming and its overcrowded housing conditions. Even when focus group moderators mentioned that the bird flu was also a significant problem for organic farmers with outdoor chicken flocks since the bird flu often spreads from wild to domestic birds, their assessment did not change. Overall and across various scenarios, laypeople tended to assess gene editing as a technology that was only needed because of extensive factory farming.[3] Many argued that instead of such a superficial technological fix, what was really needed was a fundamental change in agricultural production toward more sustainable, small-scale agriculture and better living conditions for animals. The notion that this type of agriculture could also benefit from gene editing technology received little attention from focus group participants.

[3]These results correspond to similar findings by Middelveld and Macnaghten (2021) based on focus group discussions with Dutch publics.

Next, we presented results from our interviews with small to medium-scale farmers in Bavaria (Müller et al., 2021; Feiler et al., forthcoming). In these interviews, we discussed similar application scenarios with farmers as were discussed with laypeople in the focus groups. Interestingly, assessments diverged significantly. A majority of farmers in the interview sample (11 out of 18) had a very positive stance toward gene editing. They saw the technology as a possibility to reduce threats to their livelihoods, such as disease outbreaks, and to counteract hereditary defects that have accumulated in livestock populations due to the limitations of traditional breeding techniques, while at the same time offering a tool to improve animal welfare and possibly the environmental footprint of their businesses. Many did not see a significant difference between traditional and molecular breeding techniques and welcomed the more directed character of the latter. However, while they were fairly enthusiastic about the technology as such, they also conceived of themselves as highly vulnerable to public opinion. Only if consumers evaluated the technology positively, farmers argued, would it be possible for them to employ gene editing.

After we presented these results to the consortium at the workshop and conducted a brief general questions and answers session, we split the consortium members into three smaller inter- and transdisciplinary groups of 5–7 people to discuss what these results meant for them in terms of possible futures for gene editing in livestock agriculture in Bavaria and what a responsible approach to further developing this technology might look like. After these 30-min breakout groups, we all reconvened, discussed the results of the breakout groups, and any remaining topics. It was in this section, and particularly through the responses and accounts of the agricultural stakeholders, that tensions between the mission of the project and the dynamics in the wider field of agricultural policy became visible. The debate about these tensions ultimately served to deconstruct the term "public acceptance" that had so far often characterized the narratives and concerns of agricultural stakeholders' and scientists alike. In what follows, we recount and analyze these crucial accounts by the agricultural stakeholders during the workshop.

The agricultural stakeholders responded to and discussed primarily two aspects of the results: firstly, that the public operated with a clear distinction between factory farming on the one hand, which the public viewed highly negative and which they argued should not be supported further by the introduction of new technological fixes such as gene editing; and, on the other hand, the public imagination of sustainable and organic farming, which was often imagined as a return to traditional farming methods and connected to idyllic countryside scenes with small, local farms and free-ranging animals in laypersons' accounts. Secondly, agricultural stakeholders focused their discussion on the generally positive assessment of gene editing by small- and medium-scale farmers and why they might see gene editing technologies as an important opportunity to address their everyday challenges. By focusing on these two aspects and their connections in the breakout groups and final discussion, agricultural stakeholders performed an important analysis of how both of these positions might have been generated and co-produced by the discourses and actions of the wider agricultural policy field in Bavaria and beyond, i.e., on national and European levels.

To begin with, the agricultural stakeholders outlined what they perceived as the key pressures on farmers in Bavaria emanating from the current agricultural policy field: to either constantly grow bigger, increase the number of animals and production, or, to a lesser extent, to transition to organic farming, which might allow them to sell products at a somewhat higher price. These two options would be privileged both by the government's and retailers' current incentives—a bifurcation in policy field incentives as well as in farming practices that has been noted in other national contexts, too (see, e.g., Baur, 2020 for the US). In the Bavarian context, both options still often meant that farmers cannot support themselves through farming alone and must hold additional jobs since market prices for their products are too low. Importantly, agricultural stakeholders emphasized that both versions of farming—the farms that grow bigger and the organic farms—often do not fit the images that circulate in public discourses. Neither would the "bigger" farms in Bavaria, which are still small- to medium-scale farms in the context of international industrial agriculture, be equivalent to large-scale factory farms, its practices and images that circulate in public media. Nor would organic farming necessarily comply with the idyllic imagery that characterizes TV advertisements and packaging materials for organic products. None of these popular images would accurately represent the reality of farming in Bavaria. The agricultural stakeholders argued that this disconnect of image and reality would lead to skewed consumer perspectives on current practices and future possibilities in livestock agriculture and would limit opportunities for a constructive dialogue with the public.

In a second and related step, agricultural stakeholders then elaborated that they understood farmers' positive appraisal of gene editing both as a genuine interest in the technology and as an expression of the difficult socio-economic situation in which many farmers find themselves. This difficult situation would be caused by the policy field pressures outlined above, but also by an additional aspect of the agricultural policy field in Germany, which are increasingly stricter animal health and environmental protection regulations. While market prices for their products were low, farmers would still be expected to upgrade their facilities and practices to, for example, decrease the use of antibiotics and other medications or reduce the environmental footprint of their farms. A technology that promises disease resistance or other avenues to more sustainable farming would, under these circumstances, of course, become a beacon of hope for farmers.

Thirdly, agricultural stakeholders outlined that they considered themselves poorly represented by current agricultural spokespeople on the Bavarian and national levels, which made a difficult situation worse. Official organizations would mainly represent the interests of large-scale farmers and would fail to address the challenges of small- to medium-scale

farming. This would have motivated the recent emergence of protest movements in the agricultural community, such as *Land schafft Verbindung*[4] in Germany in 2019, a grass roots movement whose name can be roughly translated as "Soil Creates Connection[5]". This movement organized so-called farmers' strikes, during which farmers across Germany rode their tractors into cities and blocked traffic for hours to draw attention to their difficult socio-economic situation (ZDF heute, 2019). Following the motto "Let's talk with each other instead of about each other," *Land schafft Verbindung* aimed to initiate dialogue with the public and to dismantle prejudice against farmers and misconceptions about farming practices. One of the misconceptions they aimed to address was exactly the above-mentioned dichotomy of industrial vs. organic farming and the issue of farming practices that fall into neither category. Under the header of "Neither idyllic nor industrial: we show you the realities of primary agricultural production," the movement wanted to open up possibilities for the wider public to become familiar with contemporary agricultural practices beyond media reports and advertisements. However, the movement has since died down somewhat due to the COVID-19 crisis and has also splintered along contemporary political fault lines.

The agricultural stakeholders argued that the combination of the factors outlined above—the public misperception of farming practices, policy field pressures that encourage bifurcation into large industrial farms and possibly small-scale organic farms, and the associated socio-economic precarity of many farmers, and a perceived low level of political representation—would increase the perceived (and quite possibly factual) dependency on consumer opinion among farmers. It is within the context of this complex understanding of the Bavarian agricultural policy field that agricultural stakeholders situate the tensions between farmers' interest in gene editing technologies and the public rejection of these technologies. Lack of public acceptance for gene editing technologies then becomes part of a larger political, social, and economic dynamic, which has, from the perspective of agricultural stakeholders, led to a profound alienation between the farming community and the wider public, which affects farmers' abilities to adopt gene editing technologies but also affects their lives and livelihood in many other and often more substantial ways. It is unsurprising that at the end of the workshop, key considerations about how to move forward focused not necessarily exclusively or even primarily on the gene editing technologies. Rather, they focused on how the actors that were assembled at the workshop—life scientists, social scientists, legal scholars, and agricultural stakeholders—could help to facilitate a much-needed dialogue between agricultural practitioners and the public about the present practices and future possibilities of agriculture in Bavarian, of which one aspect could be the use of novel technologies such as gene editing with CRISPR-Cas9.

[4]landschafftverbindung.org

[5]"*Land*" in German is a multifaceted term: it can mean country, nation, land, ground, and many more related terms. In this translation we opted for soil to stress the agricultural connect of how the term is used here.

DISCUSSION AND CONCLUSIONS

We started this article by drawing attention to tensions between the orientations of science and technology policy and agricultural policy in Bavaria in the field of gene editing technology for livestock agriculture. While stakeholders in science and technology policy have identified gene editing in livestock agriculture as a worthwhile topic to support because it aligns well with Bavaria's strategy to position itself as an innovative high-tech state, the discourses and actions of state and non-state actors in the agricultural policy field limit the practical possibilities of implementing research results successfully in Bavarian agriculture. While conflicts between the goals and practices of different policy fields are, as such, not unusual, what we want to explore in this section is the question of what tensions between policy fields might mean for the possibility to conduct RRI type research with stakeholders from different fields "responsibly".

RRI type research usually aims to involve public stakeholders in research and innovation projects in order to incorporate their situated needs and concerns early in the development of novel bodies of knowledge and new technologies and create tangible benefits for the stakeholders (Stilgoe et al., 2013). In this sense, many RRI projects involve a certain amount of knowledge and/or technology co-creation between researchers and public stakeholders. In the case of our project, this particularly concerned the co-design of editing targets between life scientists and representatives of local breeding associations to meet the needs of small- and medium-scale farmers in Bavaria by focusing specifically on conveying resistances to certain common diseases in relevant livestock animals. Furthermore, social scientists were invited to become part of the project team not least to address the agricultural stakeholders' concerns about public opinion and "technology acceptance".

The project was, on many levels, a success. Targets were effectively identified, and proof-of-concept experiments were successfully performed. Some of the project researchers are certain that the results of the project could be implemented in Bavarian livestock breeding in just a few years. However, it is highly unlikely that this will happen—a fact that most agricultural stakeholders involved in the project were quite certain about before the project even started. The fact that they participated in and supported the project can be explained by their personal ties to the researchers with whom they previously worked with on less controversial topics (and in some cases trained and studied with) and through their genuine interest in the technology. However, what does such an odd constellation—to work toward the development of a technology that key members of the consortium believe will never be implemented in this national and regional context—mean for the social science researchers, who have been brought in to add a second "R", that is "responsible", to "research and innovation"? If responsibility means to understand and meet the needs of the public stakeholders who might be affected by a new technology, what might it mean in this specific context?

RRI research, and specifically co-creation activities, have recently been criticized for emphasizing technological solutions to societal problems to the detriment of social solutions (Müller et al., 2021; Timmermans and Blok, 2021). Social science

researchers have critically reflected upon what it means to be involved in such projects and have discussed if and how they could use their role to broaden the spectrum of problem definitions and solutions constructed in RRI projects (Conley and York, 2020; Rueß and Müller, forthcoming). We believe that a tentative answer to the question above concerning what responsible (social science) research in the context of our, and quite possibly many other projects, might mean is connected to this debate, though situated slightly differently. In the context of our project, the public stakeholders have many pressing problems. Their current (and quite possibly future) inability to use gene editing technology to improve their livestock is only a minor one in this context, and possibly more of an illustration of their difficult situation than an actual problem. They are thus unlikely to benefit from the project—while the researchers, including the social science researchers, have benefitted significantly in terms of research funding, publications, and reputation. The agricultural stakeholders might benefit in small ways by continuing to cultivate positive relationships with (life science) researchers, who are important collaboration partners for them regarding other technological needs (e.g., genetic sequencing). However, overall, the benefits are clearly skewed in favor of the research actors.

Other scholars, such as de Hoop et al. (2016), have drawn attention to these paradoxical situations that can arise in RRI projects, where even despite a degree of alignment between the scientific and public stakeholders' interests within the project, wider societal contexts and the roles these stakeholders hold in these contexts make it a virtual impossibility that public stakeholders will ultimately benefit from the project in any significant way. Drawing on their own field work on farmer-researcher collaborations in the biofuel sector in India, they argue convincingly that these wider constraints need to be taken into account and taken seriously as limitations for conducting RRI responsibly. For the agricultural sector, Rose and Chilvers (2018) have recently noted that, firstly, what RRI might look like in agricultural contexts is not yet well developed, and, secondly, that any RRI activity in this sector must take a systemic perspective on agriculture and its social and political dynamics in order to succeed. Yet, what if, as de Hoop et al. (2016) find in their case, an analysis of these systemic factors implies that it will be impossible to succeed, i.e., that it will be impossible to live up to the RRI expectation of creating significant benefit for public stakeholders? Should we then resort to a position of "innovating responsibly—or not at all" as de Hoop et al. (2016, p. 129) suggest?

There is of course no "one size fits all" answer to this question. Moreover, it is in the nature of research that many systemic constraints that inhibit responsible research and innovation will only come to the fore during the research process and not beforehand. Yet, as responsiveness is one of the key characteristics of RRI, the question remains how researchers, and maybe particularly STS and other social scientists involved in RRI project, can respond to these situations as they emerge. We suggest two avenues, not as an exclusive enumeration of possibilities, but as a starting point for further debate.

Firstly, we suggest that one possibility to tip the scales slightly in the direction of creating public stakeholder benefit could be to largely abandon the original problem and solution framing of the RRI project (i.e., in our case, the focus on gene editing technology) and instead follow the public stakeholders' problem definition in order to conceive positive interventions. This might be more easily possible for the social scientists in a project than for natural scientists or engineers, whose livelihoods might be more closely tied to the original problem framing. In our case, this implied shifting the focus of our attention away from the future of gene editing in Bavaria toward the wider question of the relationship between farmers, the public, and the agricultural policy field. In this new framing, questions of technology might still play a role but they have moved away from the center. For STS scholars, this might mean that they have to go off script and leave familiar territory by moving questions of science and technology backstage, possibly even reaching out to scholars from other fields to complement their expertise as the focus of inquiry shifts. It might mean recognizing that we might not have as much to contribute to the life worlds of the public actors we intended to support and care for as we hoped. In our specific case, our contributions are certainly modest at best and remain limited to two activities. First, we reframed the problem in all project reports from a question of "technology acceptance" toward understanding attitudes regarding gene editing technology among farmers and the lay public as shaped in non-trivial ways by the current discourses and actions in the agricultural policy field in Bavaria, Germany, and Europe. We proposed that future research projects should focus on exploring relationships between agricultural communities and publics in Bavaria and examine co-existing and competing visions for the future of agriculture in Bavarian society. Through these actions, we aimed to decenter gene editing technology and instead to shift focus on key issues that concerned the public stakeholders in our project and which ultimately constituted the wider contexts of any use of genetic technology in Bavarian agriculture. As another activity, all project partners committed to organizing a public event and workshop on the topics of concern to the public stakeholders. All researchers further committed to using their networks and institutional reputation to widen the debate and access audiences beyond the circles usually accessible to the agricultural stakeholders.[6]

A second important way for social scientists to respond to situations in RRI projects, where benefits for public stakeholders remain limited, is to analyze and publish about these instances. As de Hoop et al. (2016) argue, there is, to date, "relatively little work on [R]RI's limitations and failures" (p. 112). Similarly, Rose and Chilvers (2018) argue, in reference to Macnaghten's work (Macnaghten, 2016), that "research needs to assess whether responsible innovation frameworks make a difference in practice" (p. 5). de Hoop et al. (2016) also remark that researchers often tend to report the outcomes of RRI projects in an overly positive way in order to ensure future funding. This can also hold true for social science researchers, who often, possibly even more than natural science or engineering researchers, depend on RRI funding sources.

[6]Due to the COVID-19 pandemic, this event has not yet taken place, as we consider it inadvisable to conduct the event online.

Yet, analyzing and sharing situated experiences of limitation is important for the further development of RRI practices and should, where possible, be encouraged. It is important to note that this is not synonymous with attributing wrongdoing to the stakeholders who were involved in the RRI process. In our case, the different stakeholders authentically engaged with each other and implemented RRI principles effectively—still, contextual factors, in this case the dynamics of the wider agricultural policy field, limit the possibilities for the public stakeholders to significantly benefit from the project's outcomes.

All of what we propose here are modest actions. However, they can still create benefits for public stakeholders in RRI projects, where this is otherwise unlikely, and inspire an RRI discourse that can face such limitations and situated constraints more openly. From personal conversations with other RRI practitioners and researchers, we are well aware that such situations are not uncommon, however, the whats and whys of these situations can differ significantly. Mapping the limitations of concurrent RRI practices and categorizing different types of constraints thus emerges as an important field of action for RRI researchers in order to improve future practices, acknowledge their limits within specific social, economic and political contexts, and ultimately assess if innovating responsibly is possible and what it might mean in these specific contexts.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because they are confidential qualitative social science research data. We ensured participants in the informed consent forms that only project researchers would have access to the data. Requests to access the datasets should be directed to ruth.mueller@tum.de.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

RM designed the study and wrote this article. All authors were involved in conducting the empirical research and analysis that contributed to this article. All authors contributed to the article and approved the submitted version.

FUNDING

The research presented here was funded by the Bavarian Research Association (Bayerische Forschungsstiftung). We would like to thank all our project partners with whom we worked together in the FORTiGe project and the Bavarian Research Association (Bayerische Forschungsstiftung) for funding the project.

ACKNOWLEDGMENTS

We would like to thank Marco Ninow and Maximilian Braun for their assistance in conducting the project, Michael Holohan for his valuable feedback to prior versions of this article and Christina Howell for language editing.

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