Innovation and Interdependence: The Case of Gene-Editing Technology*

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Abstract

Technological breakthroughs often reshape patterns of international exchange and interdependence, posing unique challenges for governments. We argue that innovation reduces policy autonomy among national governments in two ways. First, lower barriers to entry create opportunities for forum-shopping by researchers, firms, and other actors. This facilitates regulatory arbitrage as actors evade national rules by relocating to more permissive jurisdictions. Second, public unease about new technologies creates the potential for backlash against controversial applications. This backlash can spill across borders: accidents or misuse in one jurisdiction undermine support for research and commercial development elsewhere. Together, these processes can generate inefficient cycles of accelerated progress disrupted by damaging controversies. We test these mechanisms in the case of gene editing, finding support for the theory in data on scientific employment patterns and a survey experiment examining public backlash. Our results demonstrate that technological disruption increases interdependence and undermines states' ability to regulate in isolation.

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1 Introduction

Technological innovation is a defining feature of contemporary social and economic life. Recent advances in fields like robotics, biotechnology, digital finance, and artificial intelligence promise improved welfare through enhanced health, productivity, and economic growth. They also pose significant risks: many emerging technologies can be misused to cause harm or violate ethical norms. The recent revolution in gene-editing technology, for example, has been celebrated for facilitating new medical therapies and also criticized for enabling controversial modifications of human DNA.

Governments navigate this tradeoff by regulating the development and application of emerging technologies. Regulations seek to guide the path and speed of technological progress, balancing the economic and social potential of technological change against the risk of disruption and harm. Countries often make different choices in this environment — imposing more restrictive or permissive rules on the use of a particular technology — as governments align regulations with public preferences and social norms.

In addition to provoking a regulatory choice *within* countries, technological disruption can also shape patterns of interdependence *between* them. Many technological breakthroughs lower barriers to entry, erode incumbent advantages, and expand access to more actors in more jurisdictions. For example, improvements in rocketry and control system technology have allowed new governments and private companies to participate in space exploration. Advances in 3-D printing are similarly lowering costs and expanding participation in the development of medical devices and prosthetics. Innovation in blockchain technology has enabled novel financial transactions and new opportunities to mine and trade cryptocurrencies. As technologies like these develop, countries' regulatory efforts become more closely linked via two mechanisms.

First, the reduction in entry barriers creates opportunities for forum shopping by firms

and individuals. As innovation reduces the material costs and expertise needed to participate in an industry, actors gain more freedom of movement. They may engage in regulatory arbitrage, exploiting differences in national regulations by relocating scientific and commercial development to more permissive jurisdictions. In some cases, governments will face pressure to weaken standards to lure researchers, firms, and capital from elsewhere. While regulatory arbitrage and competition are well-established features of national governance (Genschel & Plumper, 1997), we argue that technological shocks often exacerbate the problem by lowering costs and increasing cross-border mobility.

The second mechanism is rooted in public attitudes regarding emerging technologies. Because these technologies involve risks of harm or misuse, they generate apprehension among citizens and potential consumers. When controversies occur, they often spur public backlash and undermine support for related research and commercial development. We argue that backlash frequently spills across national boundaries, such that controversies in one state affect public attitudes in another. As a result, one government's decision to weaken regulation can damage confidence in the technology around the world. Unlike regulatory arbitrage, we are not aware of existing scholarship that examines spillovers in public backlash. Nonetheless, we argue that it is an important challenge in the governance of new technologies.

These mechanisms reshape the flow of people, information, and production across borders, complicating the role of national governments as they regulate emerging technologies. The most direct effect is an increase in interdependence among countries. Interdependence refers to situations in which "the ability of one participant to gain his ends is dependent to an important degree on the choices or decisions that the other participant will make" (Schelling, 1960, p.5). In other words, it entails a reduction in a state's ability to realize its goals autonomously. Both mechanisms described above weaken the power of national governments to regulate technology in isolation. Increased opportunities for arbitrage make it easier for targets of regulation to evade national rules. The potential for spillovers in public backlash

mean that effective national governance cannot insulate a country from poor regulation in another jurisdiction. These dynamics increase the need for international policy coordination to manage interdependence.

In combination, the two mechanisms create incentives for states to mismanage risk, generating inefficient cycles of accelerated progress disrupted by damaging controversies. The freedom to forum shop diminishes governments' ability to constrain the use of new technologies; it may also encourage states to compete by weakening regulatory standards. This may temporarily speed technological progress, but also increases the systemic risk of controversial accidents or misuse. These controversies, in turn, can arouse public anxiety, undermine support, and stall continued progress.

We examine these processes in the case of gene editing, a field in the midst of a technological revolution. Gene editing refers to the targeted manipulation of an organism's genetic material. The emergence of CRISPR and associated techniques in the last decade provides a dramatically more accurate, efficient, and economical method for editing genes. In recognition of the technology's revolutionary capacity for "rewriting the code of life," CRISPR architects Emmanuelle Charpentier and Jennifer Doudna received the Nobel Prize in Chemistry in 2020.[1]

The development of CRISPR dramatically expanded the application of gene-editing technology while also triggering concerns about unethical or harmful misuse. We argue these conditions will increase the two forms of interdependence described above. First, the technology encourages arbitrage among actors in science and industry. As the capital and infrastructure needed to edit genes decreases, countries with weaker regulatory environments become more attractive destinations for cutting-edge research. These countries can more easily capitalize on the scientific and economic potential of gene editing, in part by drawing human and financial capital away from countries with more stringent regulations.

[1]Royal Swedish Academy of Sciences, "Press release: the Nobel Prize in Chemistry 2020," October 2020.

Second, controversial applications of gene-editing technology generate public backlash that spans national borders. These controversies can undermine public support, reduce funding for related research, and constrain even responsible scientific activity. As a result, the field of gene-editing research has progressed in fits and starts, with periods of promising technological advancements interrupted by crises of public confidence. As clinical gene-editing applications are brought to market, lack of public trust could reduce demand for potentially life-saving therapies.

We probe these arguments with two sets of empirical tests. We first analyze a novel dataset on gene scientist employment to examine patterns of regulatory arbitrage. Specifically, we leverage the 2012 introduction of CRISPR as a temporal shock to examine how national regulation shapes the cross-border movement of gene-editing researchers. Our results are consistent with theoretical expectations: researchers are more likely to relocate to countries with weaker gene-editing regulations after 2012. We also demonstrate that, after 2012, permissive countries outperform more stringent jurisdictions in both clinical development and patent applications for gene-editing technology.

To test for spillovers in public backlash, we implement a survey experiment in which American respondents react to a hypothetical controversy involving the birth of genetically-altered infants. In addition to this basic treatment, we vary the country in which the inappropriate gene-editing activity occurred. We find that both foreign and domestic gene-editing controversies negatively affect domestic public support for gene-editing research. We find similar effects in an observational analysis of social media data following a real-life controversy in 2018.

Our paper adds to a growing literature on international competition, cooperation, and technological change (Canfil, 2021; Drezner, 2019; Milner & Solstad, 2020; Perlman, 2020). We develop a theory of technology and interdependence in a domain, biotechnology, that has been largely neglected by scholarship in international relations and political science.

While international relations scholars have paid close attention to the security implications of technological advancements (Ayoub & Payne, 2016; Buchanan & Keohane, 2015), we know less about governance of scientific issues in non-security sectors.[2] We expect biotechnology to increase in salience as governments and their citizens grapple with the unprecedented technological progress in this field.

More broadly, we identify two theoretical mechanisms — regulatory arbitrage and spillovers in public backlash — that link countries' fates as they govern emerging technologies. In doing so, we demonstrate how technological shocks interact with patterns of economic and political exchange to induce interdependence among countries (Keohane & Nye, 1977). These mechanisms have clear implications for the design of international institutions, which are likely to be charged with managing these spillovers (Koremenos *et al.*, 2001).

The following section provides background on the case of gene editing, summarizing the emergence and governance of this rapidly advancing technology. Section 3 draws on this case to develop our theory of technological innovation and international interdependence. Section 4 describes our empirical strategy and presents our findings, and section 5 concludes.

2 Gene Editing: Technological and Political Landscape

While the ability to modify genetic material is not new, scientific advances have transformed the field over the past decade. The goal of gene editing is typically to suppress or alter naturally-occurring biological traits of an organism. Historically, the field evolved from splicing together naturally-occurring genetic material (producing "recombinant" DNA) in the 1970s to using cells' own DNA-repair technology to selectively edit specific genes (using "programmable nucleases") in the early 2000s (Gupta *et al.*, 2014).

The emergence of the CRISPR method in 2012 represents a particularly significant break-

[2]For exceptions, see Oye & Wellhausen (2009) and Perlman (2020).

through in gene-editing technology. The name CRISPR — an acronym for clustered regularly interspaced short palindromic repeats — refers to a series of repeating DNA sequences originally found in bacteria. These sequences provide bacteria with adaptive immunity, allowing them to recognize and destroy the DNA of harmful viruses. Scientists adapted this technique for programmable gene editing (Jinek *et al.*, 2012). CRISPR targets specific gene sequences and cleaves them with a nuclease, most commonly the Cas9 enzyme. This "CRISPR-Cas9" system is significantly more accurate, efficient, and economical than previous methods.

In the years since its development, CRISPR has become the dominant gene-editing technology (Carroll, 2018).[3] A report in Stanford Medicine notes that while "other gene-editing tools have emerged in recent years... none seems to match the precision, low cost and usability of CRISPR" (Shwartz, 2019). Like other breakthrough technologies, CRISPR dramatically reduces the costs associated with editing genes: by 2019, an RNA template that cost $1000 to design using rival technologies could be produced with CRISPR-Cas9 for $65 (Shwartz, 2019).

Lower costs have expanded the use of gene-editing technology to laboratories around the world. Diffusion is also facilitated by conditions imposed by scientific journals, which require authors to make their data and materials available to other researchers. Much of the biological material – including the plasmids used to edit genes – is handled by third-party distributors. Appendix Figure A2 displays the number of researchers registered with a popular genetic material repository by country of origin. American researchers are the largest group, followed by China, France, Japan, India, and Germany.[4] An employee of this repository estimated that 25% of requests are for transfers of CRISPR-related plasmids.[5]

[3]Figure A1 in the appendix shows the frequency of CRISPR patent applications compared to rival methods like TALENs and ZFNs.

[4]US Researchers are overwhelmingly the most frequent depositors of CRISPR plasmids (see Appendix Figure A3).

[5]Interview by authors, 11.25.2019.

Many have cheered the spread of gene-editing technology, which has stimulated a "biotechnological revolution" in basic research, clinical care, agriculture, and other fields (Knott & Doudna, 2018). Researchers routinely "knock out" genes in mice or other animals to study gene function and expression. New gene therapies are being developed to treat cancer and correct harmful genetic mutations (Khan *et al.*, 2016). Agricultural producers are applying CRISPR to both plants and livestock. Research teams have successfully altered the DNA of mosquitos to prevent the transmission of malaria (Gantz *et al.*, 2015). More recently, gene-editing technology has been used to develop diagnostic tests and treatments for COVID-19 (Straiton, 2020).

As with other technologies, however, rapid progress has been accompanied by public anxiety and fears of misuse. Concern over gene editing varies based on the type of genetic material researchers seek to alter. There is a strong norm against editing germline (heritable) cells in humans due to ethical objections, the unknown long-term effects of the changes, and the difficulty of ensuring the safety of the procedure (Miller, 2015).

Concern about inappropriate genetic modification escalated in 2018, when the Chinese scientist He Jiankui announced the birth of the world's first gene-edited infants. He used CRISPR to genetically alter several embryos in order to render them immune to HIV (Cyranoski, 2019). The revelation sparked international outcry, raising concerns about safety, consent of the participants, and the risks of modifying heritable germline cells that will pass to subsequent generations. Many questioned whether China had the institutional capacity or will to reign in potential ethical violations by its scientists.

Other concerns are linked to the purposes that gene-editing technology can serve. The potential for genetic modifications to enhance socially-desirable traits without conferring health benefits evokes the dark history of eugenics. The increased accessibility and public profile of gene-editing technology has also encouraged amateur scientists to experiment in unsafe conditions. Communities of self-proclaimed "bio-hackers" use gene-editing tools on

test animals, livestock, or even themselves (Keulartz & van den Belt, 2016).

2.1 Governance of Gene-Editing Technology

Gene editing is governed by a fragmented patchwork of norms, national laws, and international guidelines. When targeted gene editing first became feasible in the 1970s, scientists attempted to construct self-governing arrangements for gene-editing research. In 1973, leading geneticists announced a voluntary moratorium on gene-editing experiments involving certain viruses and toxins (Berg *et al.*, 1974). The moratorium was maintained for two years until it was replaced by formal guidelines adopted by the National Institutes of Health. Scientists involved in drafting the original guidelines argue that this decentralized approach was successful in constraining potentially inappropriate applications (Berg & Mertz, 2010).

In recent years, similar efforts have sought to establish new norms for the research community. A 2019 conference of geneticists called for a global five-year ban on editing DNA in human eggs, sperm, or embyros that are brought to term (Lander *et al.*, 2019). However, there is dissent about this approach even among the most prominent gene researchers (Cohen, 2019). The lack of consensus creates uncertainty about appropriate applications of gene-editing technology, potentially contributing to misuse. In addition, it is unclear whether voluntary, decentralized rules can succeed in an era when gene-editing technology is more accessible and diffusely distributed than in the 1970s.

As gene-editing technology progressed, national regulations began to supplement scientific norms. Early U.S. guidelines built upon the partial gene-editing moratorium of 1973-4 (Baskin *et al.*, 2016). Other states followed suit as the technology became more widespread. Currently, there is significant variation in the structure and rigor of national rules. Some countries, for example, maintain a legal ban on the alteration of human germline cells.[6] Some have less formal "guidelines" prohibiting germline editing, while others are more per-

[6]According to Ishii (2017), this group includes Canada, Brazil, Australia, and much of Western Europe.

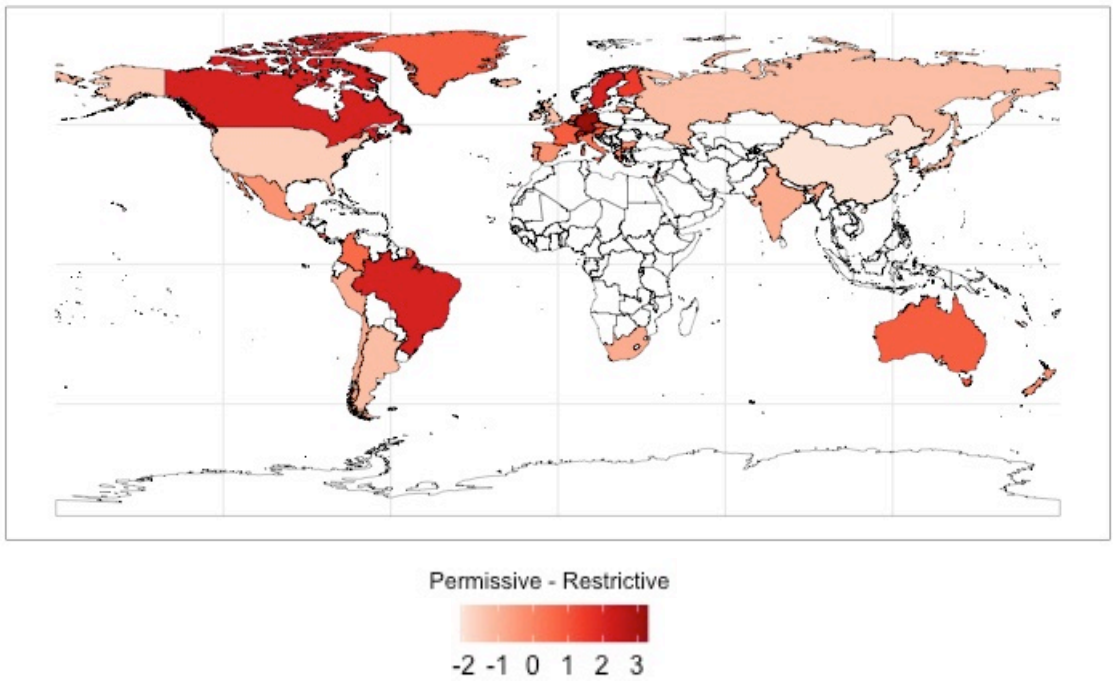

Figure 1: *National Regulation of Gene-editing Technology.* Thirty-nine countries are rated by the permissiveness of national gene-editing technology regulations. Ratings combine data from Isasi *et al.* (2016), Araki & Ishii (2014), and Baylis *et al.* (2020). See Section 4.1 for details on the coding and source data.

missive in the constraints they place on the technology (Araki & Ishii, 2014; Ishii, 2017). Figure 1 displays a composite measure of national gene-editing regulations combining information from three recent surveys of regulatory policies.[7] Countries are shaded according to regulatory rigor, with darker shades indicating more restrictive national rules.[8]

Inconsistent rules across countries stem, in part, from different historical experiences and cultural expectations regarding the appropriate use of gene-editing technology. For example, Germany's experience with unethical experiments during the Nazi regime has conditioned the state's regulation of human subjects research. South Korea developed relatively strict biological research guidelines in response to a high-profile controversy regarding the falsification of data in a cloning experiment (Resnik *et al.*, 2006). The United States maintains

[7]Source data are from Araki & Ishii (2014), Isasi *et al.* (2016), and Baylis *et al.* (2020). For details on these measures and the construction of the composite measure, see Section 4.1.

[8]Countries with no identifiable gene-editing regulations are not colored.

comparatively weaker regulations for gene editing, consistent with a policy process that is more receptive to industry influence.[9] Permissive regulations in China are driven in part by pressure to outpace Western countries in technological innovation as well as resistance to international biotechnology standards (Kleiderman & Ogbogu, 2019). In many cases, however, outdated national regulations have simply not kept up with rapid advances in the field (Baylis, 2019).

At the global level, there is growing interest in international coordination. Notably, the prospects for multilateral cooperation have not been not plagued by the political cleavages common to other issue areas (e.g., geopolitical rivalries or North-South divisions). A set of legacy international agreements, negotiated in the 1990s in reaction to concerns about cloning, provide a precedent for global governance of genetic research.[10] In recent years, however, formal international institutions have been slow to develop rules despite calls for new global standards.[11] The World Health Organization is among the few international organizations explicitly addressing the issue, releasing a set of non-binding recommendations in 2021 for appropriate oversight of human genome editing (WHO, 2021).

3 Technological Innovation & Interdependence

We argue that recent advances in gene editing, like other disruptive technologies, increase international interdependence. We identify two specific sources of interdependence — regulatory arbitrage and spillovers from public controversies — through which policy decisions in one country affect outcomes in another. In each case, we specify the underlying conditions

[9]One biotechnology expert referred to US regulation of gene-editing technology as "the Wild West" (Interview by authors, 9/21/2020).

[10]The 1997 Oviedo Convention prohibits human cloning, genetic screening for non-health purposes, and the misuse of innovations in biomedicine and bans. The 1997 Universal Declaration on the Human Genome and Human Rights and subsequent UNESCO declarations address genetic data and trade in genetic resources.

[11]In 2016, environmental activists unsuccessfully pushed for the UN Convention on Biological Diversity to expand its mandate to regulate synthetic biology and gene drive organisms.

that give rise to interdependence, draw analogies to other issue areas, and specify observable implications. While our primary focus is gene editing, we argue that these linkages are likely to recur in other emerging fields.

3.1 Regulatory Arbitrage

Gene-editing technologies are inputs to an array of commercial applications that are expected to grow substantially over the next decade. In 2019, the gene-editing market was worth approximately $3.8 billion and is projected to exceed $10 billion in the next five years (Ugalmugle & Swain, 2020).The most direct applications are in the healthcare industry, where firms are developing gene therapies to address a range of disorders and chronic illnesses. Among these are CRISPR Therapeutics, co-founded by Nobel laureate Emmanuelle Charpentier to develop gene-based medicines, which went public in 2016 and has since increased more than fivefold in market value. Other sectors like agriculture, veterinary medicine, and industrial production processes also increasingly draw on gene-editing technology (Brinegar *et al.*, 2017).

The competition for these economic returns is fierce. Patent applications associated with gene-editing technologies grew from less than 1,500 in 2000 to over 12,000 in 2019.[12] Firms are racing to develop applications and navigate regulatory hurdles to exploit the rapid market growth. As in other emerging fields, pioneer firms may gain a first-mover advantage that endures even as competitors subsequently enter the market (Lieberman & Montgomery, 1988; Agarwal & Gort, 2001).

Consequently, researchers and firms are highly motivated to accelerate the development and commercialization of gene-editing technology. One strategy for doing so is to seek out more permissive regulatory environments. While there are longstanding concerns about

[12]Data are from `lens.org` and reflect searches for "gene editing."

regulatory arbitrage in genetic research,[13] we argue that the recent revolution in gene-editing technology has substantially *increased* the potential for forum shopping. Reduced costs have expanded access to a more diverse set of actors in more jurisdictions. The ability to apply gene editing more easily and cheaply increases cross-border mobility, allowing human and financial capital to select into countries with less rigorous rules.

Accelerated forum shopping creates several problems for governments. First, it reduces a government's ability to restrict the use of the technology. Prior to recent technological breakthroughs – when altering genes required difficult and expensive recombinant DNA techniques, for example – gene editing was constrained to a handful of institutions with the funding and infrastructure to support such methods. With few alternatives, researchers were largely forced to accept the regulations that governments imposed. The technological shock significantly increased the exit options available to scientists in academia and industry. This shift allows them to evade unfavorable rules and weakened the hand of national governments.

A second problem is the potential for regulatory competition among governments. The economic returns associated with biotechnology creates pressures to lower regulatory barriers. For example, European plant breeders have pressed the EU to relax restrictions on gene editing, arguing that existing rules put them at a competitive disadvantage.[14] South Korea is reviewing its rules on gene therapy research in order to maintain its competitiveness in medical technology (Ji-young, 2017). In the United States, the government bowed to agricultural producers' demands to weaken restrictions on gene-edited crops and livestock (Cancryn & Crampton, 2021). Other countries have announced regulatory reviews or new

[13]The potential for regulatory arbitrage was raised by the geneticist Irving P. Crawford in the 1970s, citing several clinical trials that moved to Europe and South America to sidestep burdensome rules in the United States (Baskin *et al.*, 2016).

[14]See `https://www.mpg.de/13748566/position-paper-crispr.pdf`.

public initiatives to capitalize on gene-editing technologies.[15] Since lax regulations can reap economic returns, governments have an incentive to undercut each other's rules. This can generate a deregulatory spiral in which governments collectively weaken standards.

In international relations scholarship, regulatory competition is most closely associated with issues like tax policy, financial regulation, and environmental standards (Trachtman, 1993; Angelini & Cetorelli, 2003; Konisky, 2007; Genschel & Schwarz, 2011). These are policy domains in which nations differ in their regulatory approach, economic output is responsive to rules, and assets have high cross-border mobility. We argue that these conditions increasingly characterize the field of gene editing. More broadly, the conditions are likely to develop in other fields undergoing rapid technological change. Technological advancement often lowers entry barriers and encourages diffusion to a wider set of regulatory jurisdictions. It frequently occurs in industries with enormous growth potential and where initial economic advantages can yield substantial returns. As a result, we should expect emerging technologies to exhibit higher levels of regulatory arbitrage and the potential for more intense regulatory competition.[16]

An implication of this argument is that gene editing applications will advance more rapidly and with more limited oversight than a counterfactual world with fewer arbitrage opportunities. If the CRISPR revolution enables firms and researchers to relocate gene-editing activity to more permissive jurisdictions — a hypotheses we test in Section 4 — we should expect an increase in the systemic risk of accidents or misuse.

[15]Policymakers in New Zealand are reviewing the country's gene-editing regulations (Morton, 2019), and the Russian government recently announced a collaboration with Rosneft to develop gene-editing technology (Morton, 2020).

[16]Notably, other processes can sometimes counteract competitive pressures to generate a "race to the top" (Genschel & Plumper, 1997; Prakash & Potoski, 2006). In particular, if jurisdictions with sufficient market size adopt stringent rules, these can encourage higher standards elsewhere. Our argument is not that competitive pressures will dominate these countervailing forces, but that the pressure to engage in regulatory competition increases in the face of rapid technological advancement.

3.2 Spillovers in Public Controversies

The second governance challenge stems from public attitudes about emerging technologies. Like other fields, continued progress in gene editing requires maintaining a high level of public confidence. Public opinion affects the trajectory of the technology in at least three ways. First, beliefs about the safety and morality of gene editing shape consumer demand for gene therapies and other products. Aiyegbusi *et al.* (2020), for example, identify public perceptions of gene therapies as "central to their uptake and use." Second, public opinion affects the ability of firms to attract investors. Historically, controversies regarding one application of gene-editing technology have diminished investor interest more broadly (Gardner, 2020). Finally, public attitudes influence regulation, which determines the permissible ends to which the technology may be applied.

We argue that public attitudes about new technologies are often fragile. Rapid technological advances challenge existing systems of practice and thought. The ramifications of disruptive technologies frequently do not nest neatly into existing ideological or political cleavages; instead, they create unexpected coalitions and give rise to a mix of emerging public narratives. As a result, we view emerging technologies as particularly vulnerable to backlash when controversies arise. If the technology intersects traditional political divides, elites may lack incentives to provide a narrative for individuals to anchor their own beliefs (Druckman *et al.*, 2013). With no pre-existing reference frame to anchor individuals' views and moderate extreme reactions, high profile events can create quick and profound shifts in public opinion. Controversies spark public backlash, lead to reductions in public funding, and engender knee-jerk regulatory responses that constrain even responsible scientific activity.

The recent history of gene therapy provides an example of such backlash. In 1999, 18-year old Jesse Gelsinger joined a clinical trial a the University of Pennsylvania for a developmental gene therapy treatment. Unlike the other trial participants, Gelsinger suffered an unexpected

immune response that ultimately lead to his death. The tragic loss led to an immediate and precipitous drop in public support and consumer demand for gene therapies. As Jennifer Doudna recalls, the incident "made the whole field of gene therapy go away, mostly, for at least a decade. Even the term gene therapy became kind of a black label" (Rinde, 2019).

This example illustrates how an uncertain environment with few consistent cues engenders instability in public attitudes. As a result, emerging technologies that rely on public support often progress in fits and starts, with periods of promising technological advancements interrupted by crises of public confidence. There is evidence for this dynamic in the related field of genetically-modified organisms, where media exposure to controversies has been found to meaningfully affect public opinion (Prakash & Kollman, 2003; Drezner, 2008; Vigani *et al.*, 2012). Ciocca *et al.* (2021) similarly note the potential for "hype-induced backsliding" in the field of artificial intelligence.

Actors in both academia and industry are keenly aware that continued research depends on managing public anxiety about gene editing. Participants at a 2015 conference on gene editing, for example, called for slowing down the more controversial germline gene-editing research "in order to create a safe political space" (Isaacson, 2021, 288). Advocates for scientific and national regulation of gene editing frequently cite "increasing legitimacy and trust" as a primary goal (Kuzma *et al.*, 2018, 23).

Despite these calls for cautious progress, both firms and researchers have strong incentives to push the scientific frontier. The recent controversy surrounding He Jiankui's alteration of embryos triggered a new round of public concern regarding the safety and propriety of gene-editing research. Unlike the Gelsinger tragedy, however, it unleashed a response that spilled across national borders. Calls for a global moratorium on some avenues of gene-editing research swiftly followed the revelation of He's experiment (Lander *et al.*, 2019). Recognizing the potential for public backlash, leading scientists were quick to condemn the research. A senior colleague accused He of "jeopardizing the entire field of genetic engineering" (Isaacson,

2021, 306).[17]

We conceptualize backlash as a negative spillover that spans national borders. Countries receive several benefits from scientists who push the boundaries of gene-editing research. Successful innovation brings economic rewards and also enhances the prestige of the nation's scientific establishment. There are also clear costs associated with lax regulation, including the potential for domestic public backlash, but these costs are not fully internalized by the home country. Like the technology itself, backlash diffuses across borders. Controversies may damage support for gene-editing research even in jurisdictions that are comparatively well-regulated. While regulatory arbitrage has been documented in other contexts, we are not aware of existing scholarship that examines the potential for spillovers in public backlash. Nonetheless, we expect that it is an important source of interdependence that occurs whenever a technology is associated with safety risks or ethical concerns.

Though our central focus in this paper is on gene-editing technology, these theoretical mechanisms are likely to apply to many instances of technological innovation. Two scope conditions are necessary for innovation to increase the sources of interdependence described above. First, the new technology must lower barriers to entry or otherwise expand access in the industries to which it is applied. Many technological breakthroughs do this by lowering the material costs of an activity or production process; others may reduce the human capital required to participate. CRISPR satisfies this criterion by making it both easier and more efficient to edit DNA. Similarly, innovation in computing systems, telecommunications, and information technology facilitates broader participation in a range of economic pursuits. This scope condition is necessary to trigger increased arbitrage behavior, which requires the ability to apply and develop the technology in multiple jurisdictions. It also suggests technologies that concentrate rather than expand participation will not be plagued by arbitrage concerns.

[17] After initially heralding the achievement, China sentenced He and two colleagues to three years in prison for "illegal medical practice" (Cyranoski, 2020).

For example, nuclear weapons technology has diffused to relatively few countries and only to government actors, largely because states intentionally constructed high barriers to entry in this field.

Second, a technology must be susceptible to misuse, unethical applications, or harmful accidents in order to arouse public anxiety. We argue that this is a relatively common trait of emerging technologies – from nuclear energy in the 1950s to artificial intelligence today – and expect the potential for public backlash to pose a recurring challenge for technology governance.

4 Empirical Tests

We present two empirical tests of the theory outlined above. First, we leverage data on scientific employment to examine patterns of regulatory arbitrage. Because we expect the recent revolution in gene-editing technology to exacerbate forum shopping, we use the year in which CRISPR was introduced as a cutpoint in the analysis. We test whether gene-editing researchers are systematically more likely to move to countries with weaker regulations after 2012.

For the second test, we identify the presence of public backlash using an original online survey experiment on American respondents. We randomly assign information about a hypothetical gene-editing controversy and examine its effect on public support for gene-editing research and policy. The experiment varies whether the controversy occurs domestically or in a foreign country, allowing us to test whether foreign misuse of gene-editing technology affects public attitudes towards gene-editing use and policy in the United States.

4.1 Regulatory Arbitrage

We argued above that actors can evade strict regulations by relocating to jurisdictions with weaker rules, and that this behavior should increase in the wake of significant technological breakthroughs. To test this claim, we analyze employment patterns of over 100,000 gene researchers. We also look for evidence of forum shopping in the commercial development of gene-editing technology using data on clinical trials and patents.

Our independent variable is the rigor of national regulations governing gene-editing technology. We develop a composite national regulatory score drawn from three sources. First, Isasi *et al.* (2016) classify national regulations on a range of gene editing-related issues, including gene therapy, human germline editing, and genetic diagnosis. Countries are rated as "permissive," "intermediate," or "restrictive" on each issue; we transform these into a 1-3 scale of increasing regulatory rigor and average across the fields to generate a single national regulatory score. Second, Araki & Ishii (2014) provide a separate classification of countries based on the regulation of heritable genetic editing.[18] Finally, Baylis *et al.* (2020) examine national rules regarding the use of genetically modified in vitro embryos in laboratory research.[19]

These three measures are positively correlated but prioritize different applications of gene-editing technology. We combine them into a broad measure of each country's regulatory environment via principal components analysis. This provides a continuous, cross-national measure of gene-editing regulation for 39 countries that engage in gene research and clinical development.[20] Cross-national variation in these regulations is visualized in Figure 1. The

[18]The categories include "ban based on legislation," "ban based on guidelines," "restrictive," and "ambiguous," which we transform into a 1-4 scale.

[19]Baylis *et al.* (2020) categorize countries' regulatory approach as *prohibitive*, *prohibitive with exceptions*, *indeterminate*, or *permissive* based on a review of national legislation, guidelines, and codes of conduct which we transform into a 1-4 scale.

[20]The three data sources vary widely in geographic coverage. Thirty-nine countries are classified by at least two sources. For these countries, we impute the missing scores before estimating the principal components.

most restrictive regulatory environments include Germany, Sweden, Switzerland, and Brazil. The most permissive are China, Ireland, and the United States. The regulatory scores are centered at zero and range from -2.1 to 3.3.

We first examine whether gene scientists relocate to countries with more permissive regulatory standards at higher rates after the invention of CRISPR in 2012. To test this claim, we examine employment patterns of researchers who have published scientific papers in the field of gene editing. We collect these data from *PubMed*, a large database of biomedical publications. To obtain a sample of gene researchers, we extract the names and institutional affiliations of all authors who have published papers on the topic "genetic engineering" from 2002-2021.[21] The search yields approximately 120,000 papers and over 100,000 unique gene researchers.

Using this record of scholarly publications, we construct a dataset of researcher movement at the level of the directed country-dyad-year. An observation reflects the number of gene researchers who relocate from country i to country j in year t.[22] In the year 2005, for example, twelve scientists who were most recently employed in Japan published papers while employed in the United Kingdom. Another ten moved in the opposite direction, relocating from the United Kingdom to Japan. We also include observations representing scientists who remain in their "home country" (e.g., 737 researchers who were most recently employed in the UK remained there and published papers in 2005). These counts of gene scientist relocations serve as the dependent variable in the tests below.

[21] We begin in 2002 because this is the first year *PubMed* records full author names. We exclude two categories of researchers: 1) those without a listed institutional affiliation, and 2) those with very common names (appear 100 times or more in *PubMed*). We classify a researcher's country using the geographic information in their institutional affiliation.

[22] A constraint of the source data is that we only observe a scientists' country of employment in the years that they publish. Because the ability of scientists in a given country to publish research may be related to the state of gene-editing technology, we restrict the sample to researchers who published at least one paper before the introduction of CRISPR in 2012. The data therefore reflect employment relocations among gene scientists who were active researchers before the technological shock.

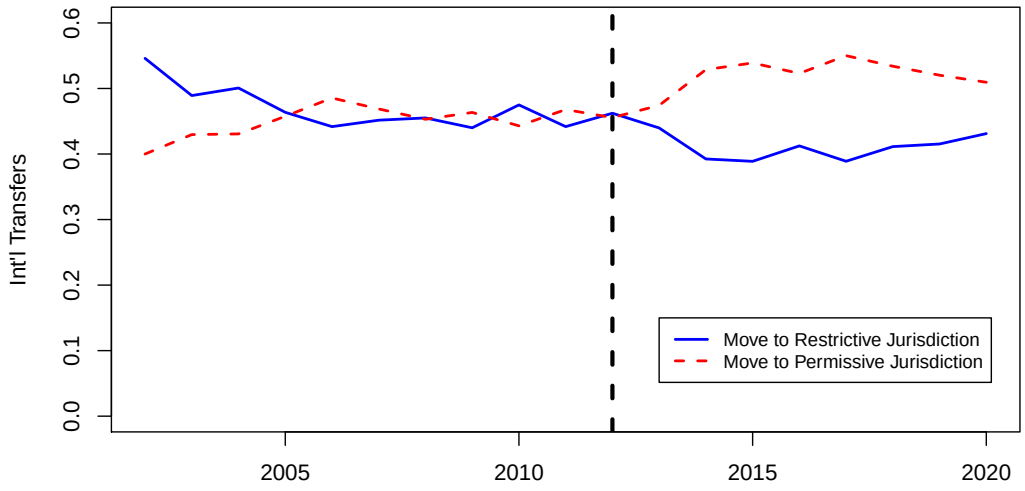

Figure 2: *International Relocation of Gene Scientists, 2001-2020.* The figure depicts the proportion of international employment transfers that represent moves to more restrictive regulatory jurisdictions (solid blue line) and those that represent moves to more permissive jurisdictions (dotted red line). Calculations by authors from *PubMed* data.

Of the 262,377 employment records we observe in the *PubMed* data, 27% represent relocation across international borders while 73% remain in their country of prior employment. International relocations occur for several reasons. Scientists move abroad in search of institutional prestige, more generous funding, familial ties, or other reasons. We argue, however, that the regulatory environment of each country shapes decisions on the margin, and that the effect of regulatory differences will be larger in the post-CRISPR period.

Figure 2 depicts the proportion of international relocations that represent movement into more restrictive vs. more permissive regulatory environments over time. Before 2012, gene scientists relocate to these jurisdictions in roughly equal measure. After the introduction of CRISPR, however, the trends diverge as more researchers forum shop "down" to weaker regulatory environments.

To test these patterns systematically, we construct a variable (`Regulatory Difference`) that subtracts the origin country regulatory score from the researcher's country of current

employment. Positive values mean that the destination country has stricter regulations than the origin country. In the statistical models below, we interact this variable with an indicator for the post-2012 era when CRISPR technology enhanced forum-shopping opportunities. These models exploit the technological shock of CRISPR to estimate how employment patterns respond to regulation in the wake of technological breakthroughs.

Control variables reflect each country's national economic output, human capital, and commitment to research funding. We include `GDP` to account for each country's economic capacity and `GDP per capita` for its level of development. We proxy scientific capital with a count of the number of patent applications in each country (`Patents`). Finally, we include a measure of `R&D` expenditure for each country. Data for all control variables are drawn from the World Bank's World Development Indicators (WDI). Separately, we add an indicator for same-country pairings to account for the high propensity of researchers to remain employed in the same country over time. We further include dyad and year fixed effects in some specifications to control for features specific to each country pair and time period.

We report the results of linear models in Table 1. Standard errors are clustered by country dyad. Column 1 presents a baseline model with the `Regulatory Difference` measure, an indicator for post-2012 (`CRISPR`), and the interaction term. The negative coefficient for `Regulatory Difference` indicates that researchers gravitate to less restrictive regulatory environments in the years before CRISPR, through the estimate is statistically significant in the fully saturated model (Column 2). More importantly, the interaction term is negative and significant, suggesting that permissive jurisdictions become substantially *more* attractive destinations after 2012. This is consistent with our theoretical expectations regarding enhanced opportunities for arbitrage in the CRISPR era. Column 2 finds broadly similar results after adding the full set of covariates as well as country and year fixed effects. Substantively, a one-unit shift in `Regulatory Difference` reduces scientific relocation by approximately 0.2 researchers per year.

	Dependent variable: Scientific Relocation	
	(1)	(2)
Regulatory Difference	-0.085^{**}	0.077
	(0.041)	(0.049)
CRISPR	0.291	-6.128^{***}
	(1.147)	(2.040)
Regulatory Difference×CRISPR	-0.117^{**}	-0.193^{*}
	(0.059)	(0.099)
Controls		✓
Dyad FE		✓
Year FE		✓
Observations	27,676	19,521

Table 1: *Employment Relocation of Gene Researchers*: Linear model estimates for the volume of gene-editing researchers who relocate to institutions in another country. Column 2 includes the following controls (not shown): *GDP origin country*, *GDP destination country*, *GDP per capita origin country*, *GDP per capita destination country*, *Patent Applications origin country*, *Patent Applications destination country*, *R&D origin country*, and *R&D destination country*. Standard errors are clustered by country dyad. Statistical significance is denoted by: *p<0.1; **p<0.05; ***p<0.01.

It is possible that permissive jurisdictions (e.g., China, Ireland, United States, and Russia) are generally more attractive destinations for scientists for reasons other than their regulatory environment. To address this, we conduct a placebo test that examines whether scientists in unrelated fields exhibit relocation patterns that correlate with national gene-editing regulations. The results, reported in Appendix Table A1, reveal no significant change in relocation patterns after 2012.

To gauge whether incentives for arbitrage extend beyond basic research to commercial development, we also analyze patterns of gene therapy clinical trials and patent applications. We find that weaker regulatory environments significantly outperform their more stringent counterparts in both clinical development and patents after 2012. See Appendix Section A.3

for these results and associated discussion.

4.2 Public Backlash

We next examine cross-national spillovers arising from public controversies via a survey experiment. The survey examines backlash among the general public in response to a hypothetical, norm-violating application of gene-editing technology. To gauge the spillover effect, we examine both the effect of controversial activity in one's own country as well as activity in a foreign country.

The online survey was conducted in July 2020 on a sample of 1,075 Americans quota-sampled to US census margins.[23] We embed an experiment in the survey designed to address two questions. First, do controversies over the use of gene editing reduce public support for the technology and its potential applications? Second, does public backlash spill across national jurisdictions?

In the experiment, all respondents receive a summary of gene-editing technology. It reads:

> All organisms, from bacteria to lizards to humans, have molecules called DNA, or deoxyribonucleic acid. These DNA molecules contain the genetic code for each organism. DNA provides the instructions that determine an organism's physical characteristics and control how it develops, functions, and reproduces.
>
> In recent years, scientists have developed new gene-editing technologies that can permanently alter an organism's DNA. These technologies allow scientists to make targeted changes to DNA molecules in plants and animals, modifying their

[23] See Appendix A.4 for full survey text and Table A2 for sample summary statistics. While the survey was fielded on a sample of 1,200 respondents, we restrict our sample to the 1,075 individuals who passed attention checks. Our survey was conducted on the platform Lucid, and our pre-registration plan can be found under EGAP 20200505AA.

biological traits. For example, scientists have edited the genes of wheat plants to make them easier to grow.

Some respondents are then randomly assigned to a treatment condition where they read about a gene-editing controversy. Among treated respondents, we randomize whether the controversy occurs in the US, UK, or China. The treatments are presented as a hypothetical news article set in near future. To increase external validity, we model the experimental intervention on the real-world controversy surrounding He Jiankui. We present the text for the UK treatment condition here:

Birth of Genetically Altered Babies in the UK Provokes Outcry

January 25, 2021

[LONDON]– A British research team announced that they have used a new gene-editing technology to alter the DNA of a group of infants. In an unprecedented intervention, scientists on the research team deleted a set of genes believed to be linked to breast and prostate cancer. The deleted genes are not considered essential to basic biological functions in humans, but the long-term effects of their removal are unclear. The research team plans to periodically examine the infants throughout their lives to assess any side effects of the genetic alteration.

The disclosure this week of the research — carried out in the UK — has sparked urgent debate about the ethics of genetic alteration. The infants' birth represents a significant and controversial leap in the use of gene-editing technology. The British study has also increased concerns about a future in which parents produce "designer babies" with selectively improved traits, such as height or intelligence.

After treatment assignment, respondents rate their agreement with the following four statements on a scale of 0 (no agreement) to 10 (complete agreement).

- Research in the US involving gene editing should be more strictly regulated.
- US patients should have access to medical treatments that involve gene editing.
- The US government should provide funding for gene editing research.
- Most US scientists conduct their research in a safe and responsible manner.

The statements estimate the extent of public confidence in the safety of gene-editing technology and support for continued development. Respondents' answers constitute our dependent variables in the analyses below.

Our theory of public backlash against emerging technologies implies two patterns of response. First, we expect that respondents who read about a controversy in their own country will be less supportive of gene-editing research. This "domestic public backlash" should heighten demand for strict regulation, depress calls for patient access to gene therapy, decrease support for funding gene-editing research, and decrease confidence in the safety of scientific research. Second, we expect foreign controversies to similarly reduce public support for gene editing among US respondents. A "public backlash spillover" occurs if the controversial use of gene editing generates a domestic backlash even when the scandal occurs in another country.

We report treatment effects for each outcome of interest in Figure 3. Coefficients in the figure represent the treatment effect of exposure to a gene-editing controversy, compared to the control (no controversy) condition.[24] Within each panel, we display the effect of a domestic controversy, a foreign controversy in the United Kingdom, and a foreign controversy in China.

We find evidence of a domestic public backlash in three of four outcomes. When American respondents read about a hypothetical misuse of gene-editing technology by American researchers, they significantly reduce support for patient access to gene therapies ($p = 0.02$)

[24]See Table A3 in the appendix for point estimates and standard errors. Table A4 reports similar results among respondents who passed an alternative attention check.

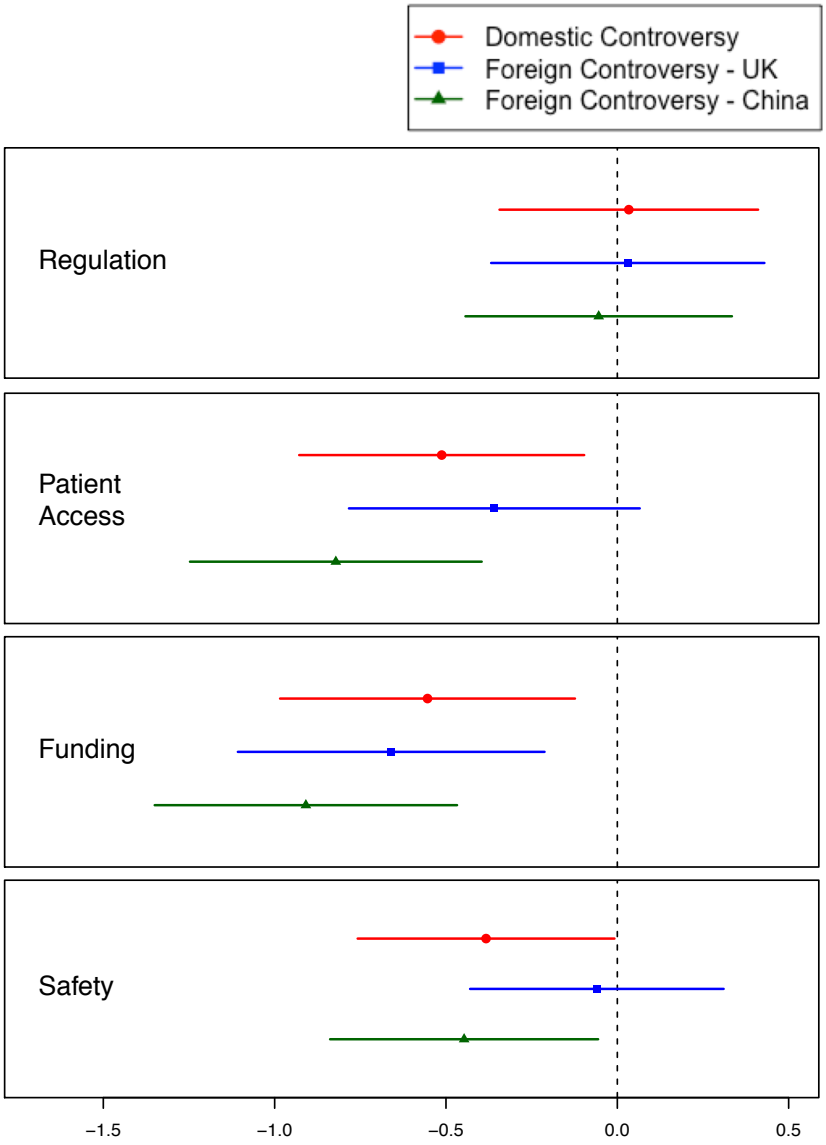

Figure 3: *Public Response to Gene-Editing Controversy.* The figure shows the treatment effect of a hypothetical gene-editing controversy in the US, UK, and China, with 95% confidence intervals. The panels report effects on the four dimensions of public support listed above.

and public funding for gene-editing research ($p < 0.01$). They also have diminished perceptions of the safety and responsibility of scientific research ($p = 0.09$) in the United States. On average, the domestic controversy treatment shifts opinion on each of these outcomes by approximately 0.5 points. Contrary to expectations, respondents do not increase demand

for strict regulations in reaction to domestic gene-editing scandals ($p = 0.61$). This null finding may reflect a ceiling effect, as even respondents in the control condition call for strict regulations in high numbers (see Appendix Figure A4 for the distribution of responses).

There is clear evidence that backlash is not limited by national jurisdiction. As in the domestic scenario, neither of the foreign scandals significantly affects attitudes about gene-editing regulation. However, support for public funding of gene-editing research significantly decreases in response to foreign controversies in the UK and China ($p < 0.01$). Respondents also reduce confidence in the responsibility of US scientists ($p = 0.07$) and support for gene therapies ($p < 0.01$) in the China condition. The UK controversy does not affect perceptions of safety but does decrease support for gene therapies ($p = 0.07$). Notably, the effects of domestic and foreign controversies are statistically indistinguishable across all four outcomes.

Together, these results suggest that the public does not discriminate between domestic and foreign research controversies. We find clear evidence that, for some public policy outcomes, the spillover effect of controversial research in one national jurisdiction negatively impacts domestic support for gene editing in another jurisdiction.

In Appendix Section A.5, we demonstrate that spillovers in public backlash occur empirically using data from Twitter posts surrounding the He Jiankui controversy. In a sample of over 50,000 tweets, we find that posts increase in volume, negative sentiment, and moral outrage following the scandal. Consistent with the spillover effect, negative sentiment and moral outrage occur at higher levels outside of the jurisdiction (China) in which the scandal occurred.

4.3 Discussion

Our findings provide evidence for two sources of interdependence that afflict national governance of gene-editing technology. We show that weaker national regulations lure scientific talent and boost gene therapy development, creating pressures for governments to engage in

regulatory competition. We also demonstrate that the risks of weak national rules are not fully internalized by the home country. If a government's permissive regulation increases the risk of inappropriate behavior, the resulting backlash spills across national boundaries.

Taken together, our results suggest that governments have compelling incentives to lower regulatory barriers beyond the level they would otherwise prefer. Each country can obtain individual economic benefits from weakening rules, while the risks of doing so are diffusely spread across multiple jurisdictions. If governments respond rationally to these incentives, effective regulation will be under-produced and the systemic risk of misuse will rise.[25] However, the resulting public backlash in domestic constituencies could reduce demand for the technology or lead to knee-jerk regulatory reactions, halting continued progress. While these inefficient boom-and-bust cycles can occur in the absence of interdependence, they are more likely to occur in the presence of regulatory arbitrage and public opinion spillovers.

By illuminating patterns of interdependence among states, our findings make an implicit case for international policy coordination. In doing so, we reinforce calls for instruments of global governance to manage "emerging technologies that affect the global commons" (Oye *et al.*, 2014). International institutions are designed to manage interdependence and reduce transaction costs (Keohane, 1984; Haggard & Simmons, 1987). The recent guidelines adopted by the World Health Organization (WHO, 2021) are consistent with this function. The recommendations establish a floor of basic ethical and safety protections and encourage harmonization of disparate rules governing the technology. If successful, this would limit the scope for regulatory competition and reduce the risk of scandalous applications. The adoption of clear norms and monitoring systems may also assuage public anxiety over misuse.

[25]While we do not directly test the effect of regulation on scientific scandals, we observe a positive correlation between weak regulatory environments and retractions in gene editing studies (see Appendix A.6).

5 Conclusion

In this paper, we put forward a theory of and provide evidence for international interdependence created by technological advancement. We demonstrate first that states are subject to regulatory arbitrage by scientists and practitioners in the field of gene-editing. The accessibility of cheap, powerful technology creates opportunities and incentives for regulatory arbitrage. To measure regulation, we construct a new index of gene-editing restrictions across three gene-editing issues: gene therapy, germline editing, and in-vitro embryonic modification. Using novel sources of data on scientific employment, gene therapy trials, and patents, we find evidence of arbitrage behavior all three domains.

We also argue that controversial applications of gene-editing technology trigger public backlash that can spill across national boundaries. As far as we are aware, we are the first to identify this theoretical mechanism that links public attitudes in one country to policy decisions in another. The effect of these controversies can be dramatic: in the history of gene editing, high-profile scandals led to collapsed public support, the abandonment of commercial applications, and harsh regulatory responses. We demonstrate the mechanism in an original survey experiment on American respondents and confirm its external validity using social media data from a real-life controversy. Our findings support the existence of a public backlash spillover that can undermine confidence in gene-editing technology.

While our tests focus on the field of gene editing, we argue these dynamics recur in the governance of disruptive technological innovations more generally. Additional work can assess the generalizability of our theory by expanding empirical tests to other fields. In addition to contemporary emerging technologies like artificial intelligence, historical disruptions such as the nuclear energy and information technology revolutions may have similarly enhanced international interdependence via these mechanisms.

More broadly, our paper helps outline a new agenda for understanding how technologies

affect interstate cooperation and the demand for global governance. Emerging technologies shape a range of transnational spillovers in addition to the two we emphasize here. Genetic manipulation of the natural environment, including vegetation or insect populations, can easily traverse national jurisdictions. Similarly, the use of digital currencies may disrupt international financial systems or exacerbate collective action problems like carbon emissions. Advancements in artificial intelligence and robotics could reshape labor demand in ways that interact with the politics of trade, human rights, or military competition. Future work should test and expand upon these effects of technological innovation.

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1 Appendix

Contents

A.1 Tables

	DV: Mental Health Scientist Relocation	
	(1)	(2)
Regulatory Difference	0.048	−42.89
	(0.047)	(33.28)
CRISPR	0.118	14.09
	(0.147)	(9.63)
Regulatory Difference × CRISPR	0.023	−0.006
	(0.078)	(0.0146)
Controls		✓
Dyad FE		✓
Year FE		✓
Observations	20,592	14,435

Table A1: *Placebo Test: Employment Relocation of Mental Health and Eating Disorder Researchers*: Linear model estimates for the volume of mental health and eating disorder researchers who relocate to institutions in another country. Column 2 includes the following controls (not shown): *GDP origin country*, *GDP destination country*, *GDP per capita origin country*, *GDP per capita destination country*, *Patent Applications origin country*, *Patent Applications destination country*, *R& D origin country*, and *R&D destination country*. Standard errors are clustered by country dyad. Statistical significance is denoted by: *p<0.1; **p<0.05; ***p<0.01.

Variable	Sample Proportion
Party ID	
Democrat	0.36
Republican	0.36
Independent	0.28
Age	
18-30	0.15
31-45	0.36
46-60	0.30
over 60	0.19
Education	
High School or Less	0.30
Some College	0.32
Bachelor's Degree	0.22
Post-Graduate	0.17
Gender	
Female	0.51
Male	0.49
Ethnicity	
White	0.83
Black or African American	0.14
Asian	0.01
Other	0.02
Hispanic	
Yes	0.13
No	0.87
Household Income	
$< \$25{,}000$	0.55
\$25-50,000	0.21
\$50-75,000	0.14
$> \$75{,}000$	0.10
Region	
Northeast	0.21
Midwest	0.20
South	0.38
West	0.22

Table A2: *Survey sample statistics*. For each category, we report the proportion of respondents who fit into the category among those that answered the relevant question.

	Dependent variable:			
	Regulations	Access	Funding	Safety
	(1)	(2)	(3)	(4)
US Controversy	0.030	−0.515**	−0.551**	−0.380**
	(0.193)	(0.213)	(0.220)	(0.192)
UK Controversy	0.037	−0.365*	−0.641***	−0.055
	(0.203)	(0.216)	(0.228)	(0.188)
China Controversy	-0.048	−0.820***	−0.910***	−0.450**
	(0.198)	(0.217)	(0.225)	(0.200)
Observations	1,197	1,193	1,198	1,199
Adjusted R^2	−0.002	0.010	0.012	0.004

Table A3: *Survey Results*. Estimated treatment effects and robust standard errors for the survey experiment. Effects are relative to the control condition (no additional informattiton). Statistical significance is denoted by: *p<0.1; **p<0.05; ***p<0.01.

	Dependent variable:			
	Regulations	Access	Funding	Safety
	(1)	(2)	(3)	(4)
US Controversy	−0.109	−0.644***	−0.572**	−0.416**
	(0.197)	(0.223)	(0.231)	(0.199)
UK Controversy	−0.531**	−0.742***	−1.165***	0.080
	(0.237)	(0.269)	(0.286)	(0.219)
China Controversy	−0.104	−1.170***	−1.347***	−0.447**
	(0.223)	(0.240)	(0.254)	(0.224)
Observations	955	952	954	955
Adjusted R^2	0.002	0.023	0.032	0.006

Table A4: *Survey Experiment Results on Respondents who pass Manipulation Check*. Results of the survey experiment on the sample of respondents who successfully pass a manipulation check. We check for attention by asking treated individuals in which country gene-editing occurred. Statistical significance is denoted by: *p<0.1; **p<0.05; ***p<0.01

A.2 Figures

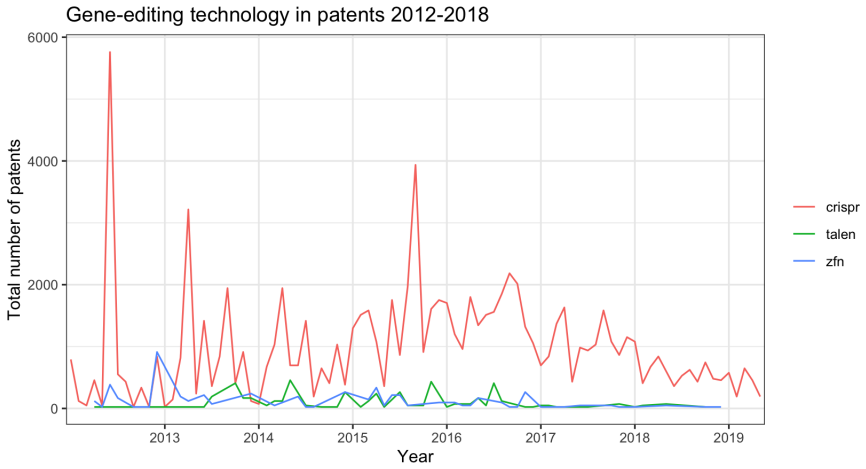

Figure A1: *Gene-editing Patent Applications, 2012-2018*: The figure displays annual patent applications related to CRISPR (red), TALENS (green), and ZFN (blue) technologies. Data from Oribit Intelligence.

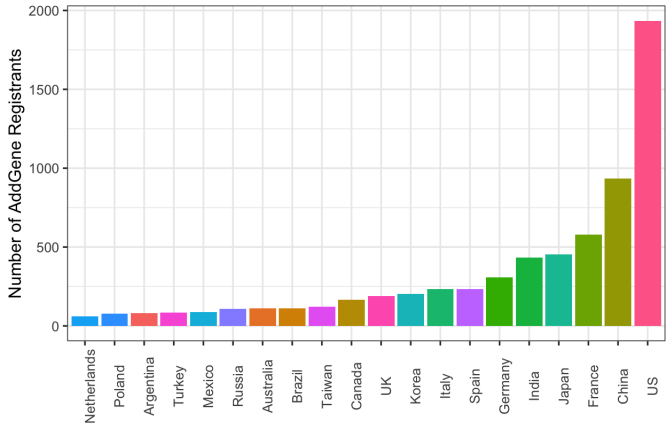

Figure A2: *AddGene Registered Researchers by Country of Origin*: Number of researchers registered on the AddGene website by country of origin. Data collected by authors. AddGene is an organization that stores and disseminates genetic material used in published studies. AddGene has served as a popular repository for CRISPR plasmids since Jinek *et al.* (2012) used it to store materials from their landmark paper. Researchers register on the AddGene website and pay a fee for the plasmid transfer. They are then free to replicate the parent study or alter the plasmids for their own research purposes. Although CRISPR-related materials are a minority of AddGene's repository, they are among the most commonly requested plasmids from researchers.

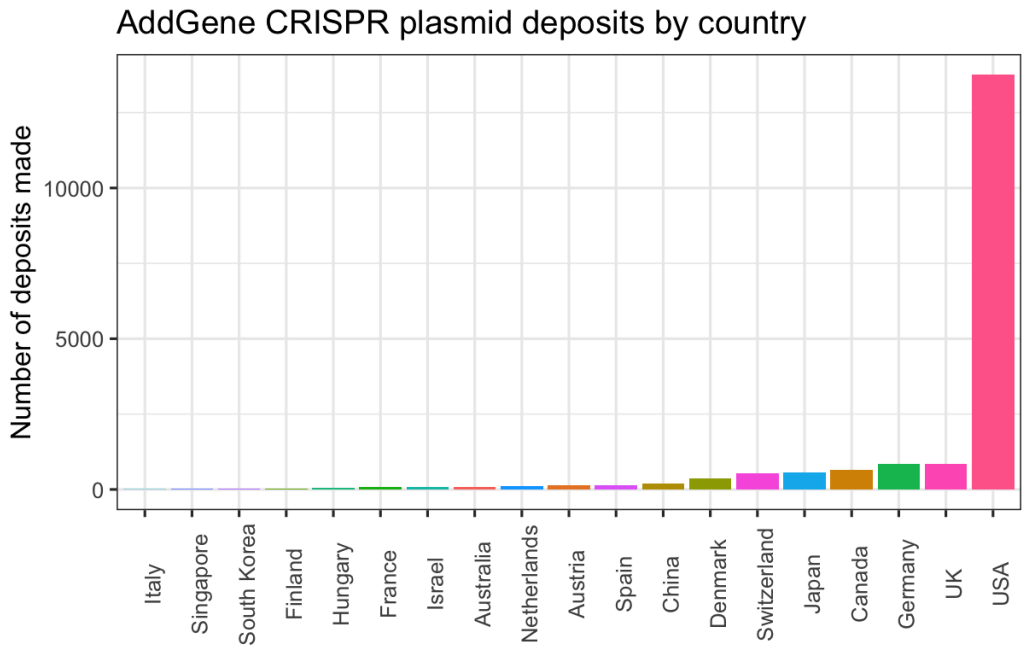

Figure A3: *AddGene depositors by Country of Origin.* Data collected by authors.

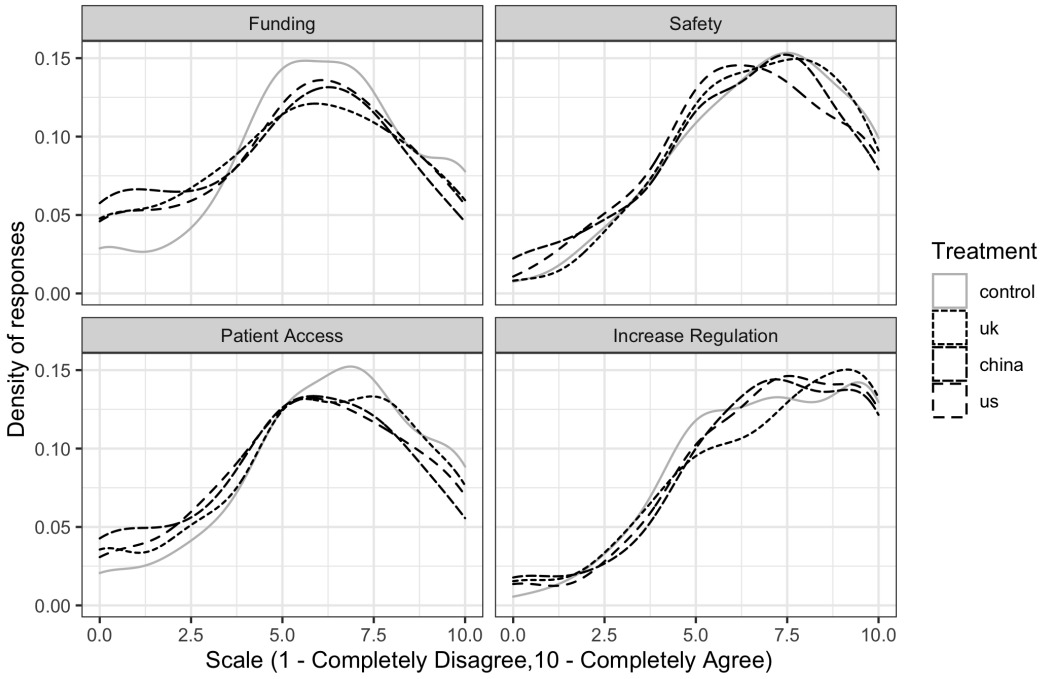

Figure A4: *Distribution of Responses for Outcome Variables.* The figure displays the distribution of responses by treatment condition for each of four outcomes.

A.3 Clinical Trial and Patent Analyses

To gauge whether our theorized mechanism extends beyond basic research to commercial development, we supplement the tests above with an examination of gene therapy clinical trials. These trials test the safety and efficacy of clinical applications of gene-editing technology. They are a necessary step to gain market authorization for gene therapies, a growing industry with high consumer demand and significant profit potential (Macpherson & Rasko, 2014; Hirakawa *et al.*, 2020). Several high-profile gene therapies have been approved following successful clinical trials (June *et al.*, 2018; Gong *et al.*, 2018), and the race to develop treatments has intensified in recent years.

We collect data on clinical trials from the Journal of Gene Medicine's "Gene Therapy Clinical Trials Worldwide" database. They capture all registered trials that perform gene therapy clinical interventions on human subjects. We structure the data at the level of the country-year, such that the outcome variable represents the number of new gene therapy trials registered in each country in each year. We restrict the sample to the 39 countries for which we have data on national regulations. The data include a total of 3,535 clinical trials.

Unlike the scientific employment tests, these data cannot definitively establish arbitrage because we cannot trace the movement of particular trials across countries over time. Instead, we simply observe the year and location in which a clinicial trial is registered. We can, however, examine whether weaker regulatory environments benefit more from the technological breakthrough than countries with more exacting rules. After 2012, technological innovation lowers the human and financial capital needed to engage in gene-editing research. Cost and expertise recede as barriers to commercial development, while regulatory restrictions are more likely to become binding constraints. We therefore expect countries with weaker regulatory jurisdictions to attract a larger share of gene therapy trials after 2012 than those in more rigorous jurisdictions.

We estimate the following linear model to determine how the regulatory environment

affects the quantity of a country's gene therapy trials.

$$\text{Trials}_{it} = \alpha + \beta_1 \text{Regulation}_i + \beta_2 \text{CRISPR}_t + \beta_3 (\text{Regulation}_i * \text{CRISPR}_t) + \beta_4 \text{X}_{it} + \epsilon_{it} \quad (1)$$

where $Trials_{it}$ are the number of gene therapy clinical trials conducted in country i in year t, $Regulation_i$ is the composite measure of regulatory rigor, $CRISPR_t$ is an indicator for the post-2012 period when CRISPR was introduced, and X_{it} is the vector of control variables described previously. As above, we expect β_3, the interaction term, to be negative and significant. This would signify that CRISPR led to the acceleration of clinical development in weak regulatory environments, compared to countries with more restrictive rules.

Table A.3.1 summarizes the results. Column 1 is a simple baseline model with national regulations, an indicator for the CRISPR era, and an interaction between them. Column 2 adds covariates and country and year fixed effects. Our core findings are consistent with theoretical expectations. In all models, the negative coefficient for `Regulation` reflects a general pattern of fewer gene therapy trials among countries with strict regulatory standards. The large and positive coefficient for `CRISPR` is consistent with an increase in the development of gene therapies after 2012. Most importantly, the interaction term `Regulation`×`CRISPR` is negative and statistically significant. This result confirms that the effect of `Regulation` on gene therapy development is greater following the technological shock of CRISPR. Substantively, a one-point reduction in regulatory rigor (e.g., moving from Finland to Italy) increases the number of gene therapy trials by approximately 1.2 per year in the pre-CRISPR era and 2.3 per year afterwards.[1] This shift is quite meaningful given the mean value of 3.1 trials per country-year.

In the final column, we estimate the same specification with the dependent variable equal to the (logged) count of gene-editing patent applications in a given country and year. The

[1]These estimates are from the model estimated in Column 1.

	Dependent variable:		
	Gene therapy trials		Patents
	(1)	(2)	(3)
Regulation	-1.207^{***}	-144.500^{***}	0.943^{**}
	(0.365)	(15.500)	(0.406)
CRISPR	2.766^{**}	3.687^{*}	-0.392^{**}
	(0.729)	(2.060)	(0.184)
Regulation×CRISPR	-1.106^{*}	-1.711^{***}	-0.074^{**}
	(0.579)	(0.376)	(0.035)
Controls		✓	✓
Country FE		✓	✓
Year FE		✓	✓
Observations	1,248	1,138	1,138
Adjusted R^2	0.038	0.270	0.711

Table A.3.1: *Effect of National Regulations on Clinical Trials, Patents.* The table displays coefficient estimates and standard errors from a linear model. Statistical significance is denoted by: *p<0.1; **p<0.05; ***p<0.01.

effect of national regulations in the post-CRISPR era is similar. After 2012, higher-regulation countries receive significantly fewer patent applications than their more permissive peers. These findings provides strong evidence that weaker regulatory environments "outperform" expectations in the commercial development of gene-editing technology. We now turn to the second hypothesized mechanism related to spillovers in public backlash.

A.4 Survey Experiment Consent and Text

In line with the APSA Principles and Guidance for Human Subjects Research, the author who provided the funding for this experiment submitted the survey protocol to the relevant Institutional Review Board (IRB) Human Subjects Committee prior to launching the survey

experiment. The IRB reviewed this survey experiment and granted an exemption under federal regulation 45 CFR 46.104 (2)(ii) (IRB Protocol ID 2000027424). The survey does not contain deceptive material, intervene in political processes, or collect sensitive and/or personally identifiable information.

Respondents were recruited through Lucid, an automated marketplace that connects researchers with online research participants. The authors compensated Lucid $1 per completed interview. Lucid contracts with suppliers who provide financial incentives to survey respondents in the form of cash, gift cards, or loyalty reward points. All respondents are voluntary participants based in the United States. For further details, see `https://luc.id/wp-content/uploads/2019/10/Lucid-IRB-Methodology.pdf`.

Before beginning, potential respondents are informed that the study is voluntary and assured that their responses will be kept confidential. We then ask for their informed consent:

> You are invited to participate in a research study that will take approximately 15 minutes to complete. You will be asked to answer some questions about yourself and your preferences.
>
> There are no known or anticipated risks to you for participating.
>
> Participation in this study is completely voluntary. You are free to decline to participate, to end participation at any time for any reason, or to refuse to answer any individual question without penalty or loss of compensation. The researcher will not know your name, and no identifying information will be connected to your survey answers in any way. The survey is therefore anonymous.
>
> If at any time you have questions or concerns about the survey or your rights or welfare as a research subject, contact [Author name] at [Author email].
>
> If you would like to talk with someone other than the researchers to discuss problems or concerns, to discuss situations in the event that a member of the research team is not available, or to discuss your rights as a research participant, you may contact the [Author's university] Human Subjects Committee, [phone number], [email]. Additional information is available at [Link to statement of research participant's rights at Author's university].
>
> If you would like to participate, simply click the 'I agree to participate' box below, then click the >> button to start the survey.

After a set of demographic questions, all respondents are provided the following information:

> Now you will read some information related to recent advances in biotechnology.
>
> All organisms, from bacteria to lizards to humans, have molecules called DNA, or deoxyribonucleic acid. These DNA molecules contain the genetic code for each organism. DNA provides the instructions that determine an organism's physical characteristics and control how it develops, functions, and reproduces.
>
> In recent years, scientists have developed new gene-editing technologies that can permanently alter an organism's DNA. These technologies allow scientists to make targeted changes to DNA molecules in plants and animals, modifying their biological traits. For example, scientists have edited the genes of wheat plants to make them easier to grow.

Respondents are then randomly assigned to one of four conditions:

1. Control - no additional information
2. Domestic Controversy
3. Foreign Controversy (UK)
4. Foreign Controversy (China)

Those assigned to conditions 2-4 additionally read a hypothetical news article regarding a gene-editing controversy. We show the text for the Foreign Controversy (UK) here.

> Below you will read a hypothetical news article about the use of gene-editing technology. The article describes events that could take place in the future. After you have read about the situation, we will ask for your opinions.
>
> **Birth of Genetically Altered Babies in the UK Provokes Outcry**
> January 25, 2021
>
> [LONDON]– A British research team announced that they have used a new gene-editing technology to alter the DNA of a group of infants. In an unprecedented intervention, scientists on the research team deleted a set of genes believed to be linked to breast and prostate cancer. The deleted genes are not considered essential to basic biological functions in humans, but the long-term effects of their removal are unclear. The research team plans to periodically examine the infants throughout their lives to assess any side effects of the genetic alteration.
>
> The disclosure this week of the research — carried out in the UK — has sparked urgent debate about the ethics of genetic alteration. The infants' birth represents a significant and controversial leap in the use of gene-editing technology. The British study has also increased concerns about a future in which parents produce "designer babies" with selectively improved traits, such as height or intelligence.

Finally, we ask respondents to rate their agreement with four statements on a scale from zero to ten.

> Please indicate your level of agreement with the following statements, with "0" representing complete disagreement and "10" representing complete agreement.
>
> - Research involving gene editing should be more strictly regulated in the US
> - US patients should have access to medical treatments that involve gene editing
> - The US government should provide funding for gene editing research
> - Most US scientists conduct their research in a safe and responsible manner

A.5 Public Backlash: social media data

We follow (Müller *et al.*, 2020) in scraping and analyzing tweets with the keyword CRISPR. Using Twitter's API through Barrie & Ho (2021)'s R package, `academictwitter`, we pulled approximately 50,000 tweets that contain the word "CRISPR" in the 50 days prior to and after the He Jiankui controversy.[2] The bottom panel of Figure A.5.1 shows a histogram of the appearance of CRISPR in tweets over this time period. Using a bag-of-words procedure, we take the average sentiment of each tweet by identifying the proportion of positive words in the tweet. Higher proportions indicate higher levels of positive sentiment. Only English-language tweets are included in the sentiment analysis. Only tweets with at least one word with a positive or negative valence are included in this sample. The top panel of Figure A.5.1 displays change in average sentiment over time.

While sentiment in tweets does capture overall public opinion of Twitter users towards CRISPR technology, new research suggests that certain forms of expression on social media are more likely to drive conversations (Brady *et al.*, 2021). In particular, tweets expressing moral outrage receive higher levels of positive feedback online and are therefore more likely to

[2]We exclude replies and retweets in our analysis.

be seen and to influence online sentiment (Brady *et al.*, 2021). We use Brady *et al.* (2021)'s measure of moral outrage to understand whether controversial events in CRISPR technology influence not only sentiment, but the type of language that drives greater engagement with the overall conversation. We note that moral outrage is a form of negative sentiment. We measure the number of words stems associated with moral outrage in each tweet. The middle panel of Figure A.5.1 displays change in moral outrage over time. Table A.5.1 reports the pre-post change in sentiment and outrage expressed in tweets.

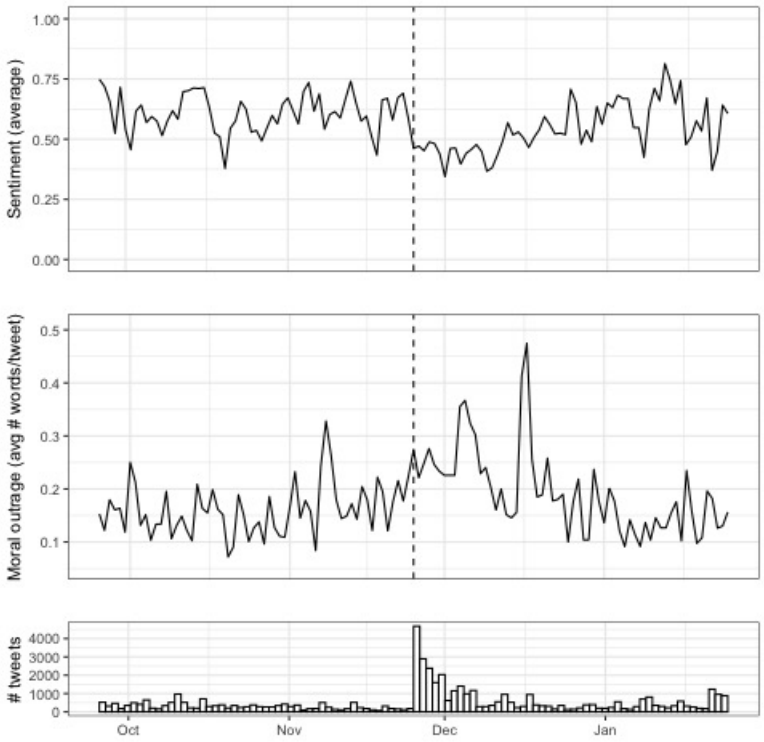

Figure A.5.1: *CRISPR tweet sentiment*: Top panel: sentiment analysis of tweets including the word "CRISPR" from September 2018 - January 2019. Higher values indicate more positive sentiment. Middle panel: moral outrage in same sample of tweets. Higher values indicate more moral outrage. Bottom panel: histogram of number of tweets per day. Dashed black line on November 26, 2018, the day the He Jiankui controversy became public. Data collected by authors.

Subsetting the data to only tweets with identifiable geolocation data for the associated Twitter user, we replicate the main analysis by user country. We limit our analysis to English-

	Dependent variable:	
	Sentiment	Moral Outrage
	(1)	(2)
Post-He Jiankui	-0.110^{***}	0.062^{***}
	(0.006)	(0.004)
Constant	0.609^{***}	0.158^{***}
	(0.005)	(0.003)
Observations	21,856	50,839
R^2	0.013	0.004
Adjusted R^2	0.013	0.004
Note:	*p<0.1; **p<0.05; ***p<0.01	

Table A.5.1: *Change in Tweet Sentiment*. Average tweet sentiment and number of expressions of moral outrage before and after the news of the He Jiankui controversy broke on November 26, 2018. *Sentiment* refers to expressions of positive sentiment and is only measured for tweets with at least one word that expresses positive or negative sentiment; positive values indicate more positive sentiment. *Moral outrage* refers to words that are categorized as expressing moral outrage and indexes the number of words per tweet that reflect this sentiment; positive values indicate increased outrage. Robust standard errors in parentheses. Sample is all English-language tweets mentioning "CRISPR" from September 2018 - January 2019.

language tweets, which likely affects the composition of countries in this sample. Figure A.5.2 displays the results for countries with more than 10,000 unique tweets that mention CRISPR. As Figure A.5.2 shows, the revelation of the gene-editing controversy produced negative sentiment in the days afterwards for every country in the sample. Importantly, the scandal did not occur in any of these countries. (China is not included in the sample as the country blocks access to Twitter for regular users.[3])

In addition to expressing a particular form of negative sentiment, posts that use the language of moral outrage also generate greater engagement in the form of likes and retweets (Brady *et al.*, 2021). Using a dictionary of moral outrage terms (e.g., "abhor", "hate",

[3] `https://help.twitter.com/en/rules-and-policies/state-affiliated-china`

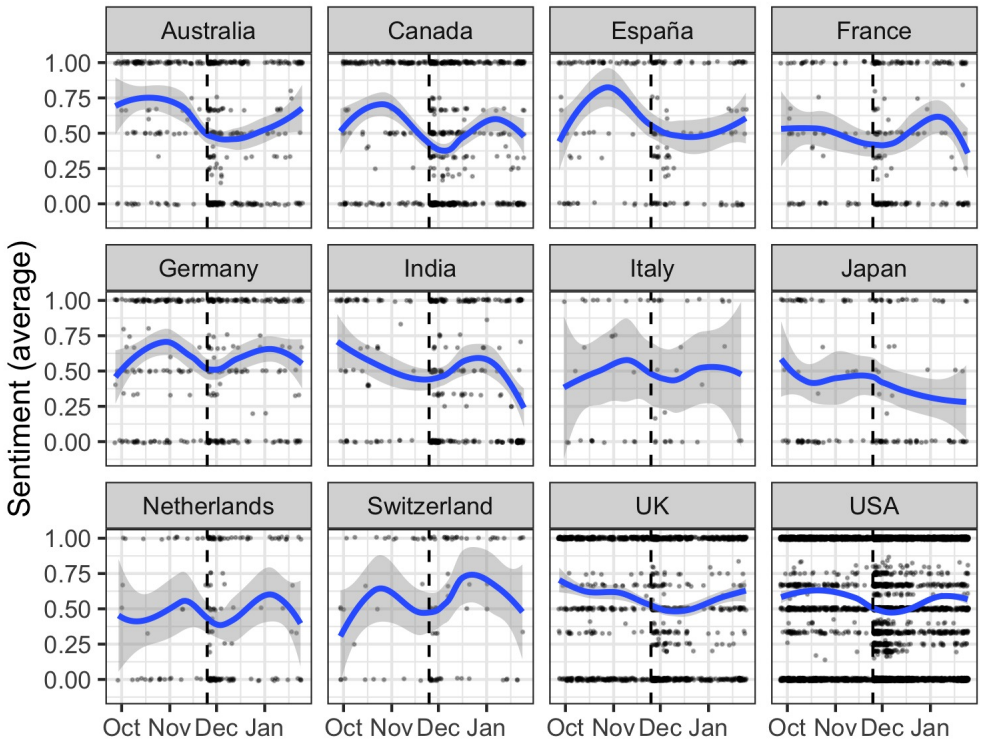

Figure A.5.2:*CRISPR tweets by location*: Sentiment analysis of tweets including the word "CRISPR" from September 2018 to January 2019 by Twitter user location. Only countries with over 10,000 CRISPR-related tweets included. Higher values indicate more positive sentiment. Blue line is a fitted loess model; grey bar indicates 95% confidence interval. Dashed black line on November 26, 2018, the day the He Jiankui controversy became public. Data collected by authors.

"shame"), we measure the extent of moral outrage expressed in tweets.The top panel of Table A.4.2 confirms that tweets that contain higher levels of moral outrage are liked and retweeted more often. Tweets with greater positive sentiment are liked more (but not retweeted more). The bottom panel shows that moral outrage tweets are not more liked or retweeted post-scandal. In contrast, negative sentiment tweets are retweeted and liked more often post-scandal. These results 1) confirm that moral outrage tweets have greater engagement in the realm of gene-editing and 2) show that negative sentiment tweets are engaged with at higher rates post-scandal. Combined with prior findings about higher numbers of negative sentiment and moral outrage tweets in response to scandal, this suggests even greater levels

of public opinion shifts to anti-gene-editing sentiment after scientific scandals. The finding is particularly salient when one considers that public policy attitudes are driven by social cues from peers in addition to elites (Kertzer & Zeitzoff, 2017).

	Dependent variable:			
	Retweets	Likes	Retweets	Likes
	(1)	(2)	(3)	(4)
Moral Outrage	0.715***	1.373***		
	(0.185)	(0.349)		
Sentiment			−0.022	0.877**
			(0.205)	(0.402)
Observations	50,839	50,839	21,856	21,856
	(5)	(6)	(7)	(8)
Moral Outrage	1.066**	2.332**		
	(0.444)	(1.023)		
Sentiment			0.556	2.035**
			(0.385)	(0.944)
Post-He Jiankui	−0.022	−0.421*	0.352	0.058
	(0.107)	(0.236)	(0.364)	(0.746)
Moral Outrage*Post-He Jiankui	−0.455	−1.214		
	(0.487)	(1.075)		
Sentiment*Post-He Jiankui			−0.846*	−1.816*
			(0.452)	(1.023)
Observations	50,839	50,839	21,856	21,856

Table A.5.2: *Tweet Virality.* Correlation between average tweet sentiment and number of expressions of moral outrage with tweet virality (likes and retweets). *Sentiment* refers to expressions of positive sentiment and is only measured for tweets with at least one word that expresses positive or negative sentiment; positive values indicate more positive sentiment. *Moral outrage* refers to words that are categorized as expressing moral outrage and indexes the number of words per tweet that reflect this sentiment; positive values indicate increased outrage. Robust standard errors in parentheses. Sample is all tweets mentioning "CRISPR" from 9-25-2018 to 1-25-2019. Bottom panel displays pre-post results on virality.

These results confirm the external validity of our experimental findings. The He Jiankui scandal was salient to the public as evidenced by the steep increase in tweets about gene-editing technology after the scandal was made public. These tweets were also more negative and contained higher levels of moral outrage. Finally, geo-located tweets confirm that the scandal, which occurred in China, had effects on international public opinion about gene-editing technology.

A.6 Regulations and Scientific Retractions

We directly test for a correlation between regulatory stringency and scientific scandals through data on scientific retractions in the field of genetic editing. Retractions may occur for many reasons including ethical malfeasance, data manipulation, and data errors. Retractions are characterized as scandals in the scientific community (Azoulay *et al.*, 2017) and have significant negative effects on the field of study in which they occur (Azoulay *et al.*, 2015). Within our sample of gene-editing papers, 674 unique scientists were involved in 121 redacted papers as indicated in the *PubMed* database. We identify a clear negative correlation between the level of regulation in a country and the number of redactions ($\rho = -0.39$, $p = 0.02$) as well as the proportion of retracted papers ($\rho = -0.28$, $p = 0.12$) in a given country. Figure A.6.1 visualizes these relationships.

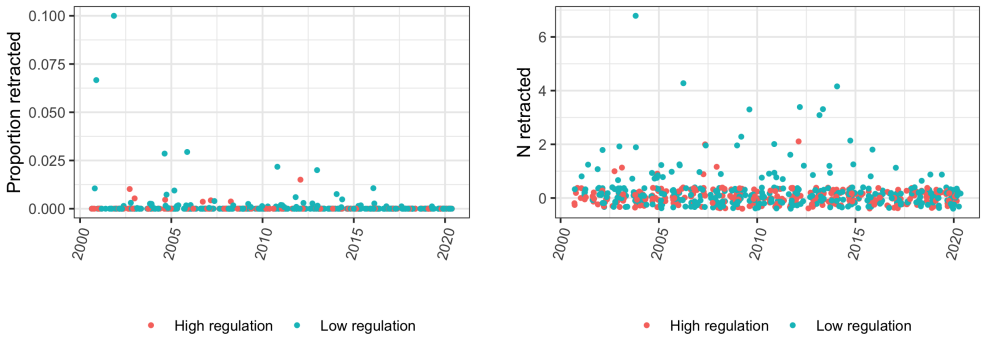

Figure A.6.1: *Regulations and Scientific Retractions.* Left panel depicts proportion of papers published by scientists located in a given country in a given year that were retracted. Right panel depicts raw numbers of retracted papers by country-year.

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