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The role of externalities and uncertainty in policy design: evidence from the regulation of genome editing

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ABSTRACT

Externalities and uncertainty play an important role in the design of regulatory policies. Regulatory tools must be selected while taking into consideration the side-effects that regulated products or services have on other individuals and on the environment. This study investigates the externalities and uncertainty that arise from the use of genome editing (with specific reference to CRISPR technique) and how they relate to regulatory policy design choices. Building on evidence from genome editing regulation and on the NATO (Nodality, Authority, Treasure and Organization) policy tools framework, this study argues that a mix of regulatory tools is required to tackle externalities of genome editing applications and to cope with sources of uncertainty about their beneficial, neutral and harmful side-effects. The study provides some recommendations to policy-makers about reducing uncertainty, diversifying regulatory tools over time, and communicating to the public about features of genetically edited products.

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1. Introduction

The design of public policies requires careful consideration of the properties of policy subsystems (Sabatier 1988; Weible 2005; Weible and Sabatier 2017). Properties of policy subsystems include externalities, which have been long recognized as crucial features of economic activity (Cornes and Sandler 1996). Externalities arise when production or consumption activities bring about side-effects to other actors but those who undertake the acts of production or consumption themselves (Ayres and Kneese 1969). The presence of externalities poses special challenges to the design of public policies (Candela, Castellani, and Dieci 2008). Regulatory tools that are intended to steer the conduct of a particular actor may have repercussions on other actors that are affected by the particular actor's externalities. The pursuit of a specific policy goal may trigger side-effects that compromise the attainment of other policy goals. It is also

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possible that the pursuit of a specific policy goal is attained as a side-effect of other policies that target other individuals or groups.

Externalities pose challenges to policy design because they can make policy subsystems operate in ways that diverge from a mechanistic process where cause-effect relationships are linear and plainly understood (Capano and Howlett 2021; Capano et al. 2019). Policy designers typically face uncertainties about the direction and intensity of externalities (Kwakkel, Haasnoot, and Walker 2016). The regulation of emerging technologies, in particular, is fraught with uncertainties about whether applications bring about positive, neutral or negative effects to individuals and to the environment (Mandel 2009; Roca et al. 2017). Some applications of emerging technologies may have dangerous side-effects like, for instance, when novel toxic substances are released into the environment or when innovative digital financial products compromise the stability of the financial system. A deeper understanding of the role of externalities and uncertainty helps design policies that stimulate the use of emerging technologies while limiting their unwelcome side-effects.

This study aims to investigate the role of externalities and uncertainty in policy design by investigating their role in the regulation of genome editing with specific reference to CRISPR technique. Discovered in 2012, CRISPR (which stands as the acronym of Clustered Regularly Interspaced Short Palindromic Repeats) allows the manipulation of the genome in a way that is more accurate, precise and efficient than former methods. CRISPR is selected as a case of emerging technology whose effects on individuals and the environment are still relatively unexplored (Asquer and Krachkovskaya 2020; Sarewitz 2015). The next section will present details of the method followed in this study. Section three will discuss the challenge of regulating genome editing. Section four will develop a taxonomy of externalities of genome editing and discuss the role of uncertainty in the design of regulation of genome editing. The last sections will discuss the findings and then draw the conclusions.

2. Research method

This research consists of a case study of CRISPR regulation, which is selected as an instance of regulatory policy of emerging technologies. The use of case studies in design research has been widely discussed (Chow 2008; Teegavarapu, Summers, and Mocko 2008; Hathaway and Norton 2018). Case studies provide a way to investigate in detail how outcomes originate from the joint occurrence of process features and context factors (Barzelay 2007). Yet, as design-oriented sciences are concerned with creating possible futures (Krippendorff 2005) than describing or explaining present or past state of affairs, the case study of CRISPR regulation is used here with the intent of providing an assessment of the tools that policy designers can use to regulate emerging technologies.

Evidence of regulatory policies on CRISPR was collected from secondary sources. Secondary sources consisted of academic papers, policy papers and newspaper articles published on CRISPR regulation between 2012 and 2021 in a few selected main economies, namely the US, the EU, the UK, Canada and Australia. A search for academic papers in social sciences resulted in a selection of 182 articles from Web of Science and

(partially overlapping) 293 articles from Scopus. A search for policy briefs resulted in a selection of 76 documents from OECD, 171 documents from UN FAO and 1 from UN WHO. A search for parliamentary publications and transcripts (Congressional Records and Hansard) resulted in a selection of 74 documents from the US, 55 documents from the EU, 43 documents from the UK, 16 documents from Australia and 7 documents from Canada. A search in Access World News resulted in 375 newspaper articles. Sources were coded independently by the authors and then coding differences were discussed and reconciled.

3. The challenge of regulating genome editing

Genome editing is a set of techniques that enables scientists to manipulate selected parts of a genome in a targeted way. Various genome editing techniques exist (e.g. zinc-finger nucleases or ZFN and transcription activator-like effector nucleases or TALEN), but CRISPR quickly revolutionized the field and opened up a plethora of applications, from disease diagnostic (Chertow 2018) to therapies (Lee and Kim 2019), from crop productivity (Chen et al. 2019) to pest control (McFarlane, Whitelaw, and Lillico 2018). During the last decade, investments into biotechnology companies (most notably, Caribou Biosciences, CRISPR Therapeutics, Intella Therapeutics, ERS Genomics and Editas Medicine; Cohen 2017) skyrocketed. Potential developments offered by CRISPR include, for example, growing organs for xenogenic transplantation, combating cancer and treating genetic diseases.

The rise of CRISPR poses various sources of threats and dangers (Evitt, Mascharak, and Altman 2015, Herring and Paarlberg 2016). Genome edits may result in mosaicism, toxicity and other unwelcome genetic defects (Mehravar et al. 2019). The release of genetically edited organisms in the environment may compromise existing ecosystems and survival of species (Webber, Raghu, and Edwards 2015). Applications of genome editing to humans may help pursue eugenic programs and exacerbate inequalities within society (Pollack 2015). Genome edits could be also carried out for deliberate harmful purposes, such as, for example, bioterrorist attacks (Kosal 2020).

At present, the regulation of genome editing is rather fragmented, uncomplete and inconsistent across countries (Entine et al. 2021; Charo and Greely 2015). In the US, genome editing is regulated by the 1986 Coordinated Framework for the Regulation of Biotechnology, which was updated following the "Memorandum on Modernizing the Regulatory System for Biotechnology Products" issued by the Executive Office of the US President in 2015 and the "Executive Order on Modernizing the Regulatory Framework for Agricultural Biotechnology Products" issued by the US President in 2019. In the EU, in 2018 the European Court of Justice (ECJ) ruled that genome editing is subjected to Directive 2001/18/EC on the deliberate release of genetically modified organisms (GMOs), which practically outlawed the marketing and importing of genetically edited products irrespective of the technique that is used to produce them. After leaving the EU in 2020, the UK considered to review regulations of genetically modified products in order to permit the use of genome editing techniques. In 2019 Australia amended existing rules on genetic modification techniques by exempting the use of genome editing that does not introduce new genetic material from approval.

Canada followed a similar approach, which was expected to amend the existing "plants with novel traits" (PNTs) framework following industry consultation in 2021. Genome editing of human embryos is generally banned or subjected to strict limitations, like, for example, in the UK where it can be used when genetic edits cannot be inherited or when embryos are genetically edited for research purposes but not implanted.

Evidence of the variety of regulations across countries suggests that policy designers can regulate the use of genome editing in different forms. At one end of a spectrum, genome editing can be subjected to an outright ban, which may arise because of an overestimation of possible negative effects of CRISPR applications (Maor 2012, 2014). At another end of the spectrum, the use of genome editing can be fully unrestrained. None of these two extreme regulatory policies seems advantageous, because they would either obstruct the development of beneficial applications or expose individuals and the environment to countless risks and hazards. Policy designers, however, can also regulate emerging technologies through a mix of policy tools. Drawing on the NATO taxonomy (Hood 1986), an indicative list of regulatory tools for CRISPR applications includes:

- *Nodality tools*: collecting information on research, development and applications of genome editing techniques and related applications, and sending out information in such forms as, for example, scientific reports, research and policy guidelines and communications to the public.
- *Authority tools*: subjecting research, development and applications of genome editing to the issue of permits by public authorities and to the compliance with procedural and substantive rules, while monitoring practices and enforcing penalties in case of violations.
- *Treasure tools*: providing subsidies (i.e. grants) to research, development and applications of genome editing, and levying taxes to discourage commercialization and consumption of unwelcome products and therapies.
- *Organization tools*: carrying out research, development and applications of genome editing in government agencies, commercializing applications or delivering them as public services, or orchestrating the development of markets of genetically edited products (e.g. by ensuring the infrastructure of patent and tort law systems).

The regulatory tools of the NATO framework can be selectively applied to different component parts of genome editing business models. Table 1 presents examples of how regulatory tools can be used to monitor, steer or hinder CRISPR applications by affecting activities that are carried out on the "input side" of business models (e.g. staffing, financing and procurement), the "output side" (e.g. delivery of products and services, licensing and marketing) and the business development activity (e.g. R&D investment). Regulatory tools that apply to the input side may consist of collecting information on procurement activity, authorizing acquisition of know-how and supplies, providing subsidies or undertaking financing and training. Regulatory tools that affect the output side may consist of communicating to the public about features of genetically edited products, providing legal protection to intellectual property, subsidizing the market for genetically edited products or making use of genetically edited

Table 1. Examples of NATO regulatory tools applied to different activities of genome editing business models.

	Activity of the regulated		
	Input side (staffing, financing and procurement)	Business development (R&D investment)	Output side (delivery, licensing, marketing)
Nodality tools	Collecting information on acquisition of know-how and supplies	Collecting information on R&D activity	Communicating to the public about features of genetically edited products
Authority tools	Prohibiting the acquisition of genome editing kits	Authorizing R&D activity	Protecting intellectual property of genetically edited products
Treasure tools	Subsidizing skilled labor provision	Providing grants or tax credits to investments in R&D	Subsidizing products, purchasing products from firms
Organization tools	Setting up education and training programs	Undertaking R&D in public sector agencies	Employing genetically edited products in the delivery of public services

products in the delivery of public services. Regulatory tools, finally, may also play a role in business development, for example by monitoring R&D activity, requiring operators to apply for authorizations before carrying out R&D, providing financial support to R&D or having government agencies directly undertake R&D in the field of genome editing.

Country experiences provide examples of regulatory tools of the NATO framework applied to genome editing. Nodality tools are employed in the monitoring of CRISPR activity, like the one carried out by the Global Observatory for Genome Editing (established in September 2020), and in the communication of genome editing to the public, like in the Genome Editing Public Engagement Synergy (GEPES) program of the National Coordinating Center for Public Engagement in the UK. Authority tools are used in the prohibition to sell do-it-yourself CRISPR kits if not warning against self-administration, which was adopted in California (Zettler, Guerrini, and Sherkow 2019); in the issue of licenses to allow genome editing of human embryos by the Human Fertilization and Embryology Authority (HFEA) in the UK; and in the (ongoing, at the time of writing) resolution of controversies over CRISPR intellectual property rights between UC Berkeley and the Broad Institute. Treasury tools are deployed in the provision of CRISPR research-related PhD scholarships in various countries and of research grants, like, for example, the Somatic Cell Genome Editing program by the National Institute of Health in the US and the Use of Genome Editing in Agriculture program by Horizon Europe. Organization tools include, for instance, the National Human Genome Research Institute in the US, which carries out activities in public engagement, funding and research.

What for do countries adopt multiple regulatory tools for genome editing? It is argued here that the variety of regulatory tools is related to the externalities and uncertainty that arise from CRISPR applications. As a platform technology, genome editing opens up several applications which may not be fully anticipated, and which may exert unforeseen effects onto individuals and the environment. Multiple regulatory tools provide a way to cope with the externalities and uncertainty posed by CRISPR applications. The following section will develop a taxonomy of externalities of CRISPR

applications and discuss the role of uncertainty in the design of regulation of genome editing.

4. Externalities and uncertainty in genome editing

Applications of genome editing may be intended to bring about beneficial or harmful effects on targets. Beneficial effects are attained, for example, in the use of genome editing for therapeutic purposes. Harmful effects may be pursued, instead, when using genome editing to create viral or bacterial agents as biological weapons. In addition, genome editing applications may have effects onto individuals and the environment that can be of beneficial, harmful or neutral sort. The combination of effects on targets and other effects results in multiple configurations that are exhibited in Table 2.

Table 2 shows six possible configurations of externalities of genome editing applications. Applications that are beneficial to both targets and others, which are labeled as "benign" ones, include, for example, the use of genome editing for developing diagnostic tools, which may result in widespread beneficial effects because of detecting and helping contain infectious diseases (Foss, Hochstrasser, and Wilson 2019). Applications that are beneficial to targets but neutral to others would not pose externalities issues, like for example the development of targeted therapies to patients (Cox, Platt, and Zhang 2015; Gori et al. 2015). Such applications may be labeled "proprietary" because intellectual propriety would be crucial to ensure that genome editing ventures take advantage of the targeted effects. Other applications, instead, may be beneficial to targets but harmful to others, such as, for example, gene drive interventions that deliver specific advantages while worsening – as an "inconsiderate" tool – the conditions of other individuals or species or the environment. Examples include the release of genetically edited animals which are intended to eradicate a particular species or contain the propagation of undesirable traits or disease, but which can also compromise the stability of ecosystems (Alphey 2016; Courtier-Orgogozo, Morizot, Boëte 2017), and the enhancement of an individual's traits which may result in the deterioration of socio-economic conditions of other individuals who are excluded from eugenic programs (Friedmann 2019).

Applications of genome editing may be also developed with the intent to deliver harmful effects to targets. Some "predatory" applications may be harmful to a target but beneficial to others, like, for example, the development of genetically edited organisms with the intent to sabotage competitors' production activities in order to attain commercial gains. Other applications, of "punitive" sort, may be harmful to a target while they do not have repercussions to others, like, for example, the development of ethnic bioweapons that would attack individuals of a particular genotype while being

Table 2. Features of genome editing applications depending on their effects on targets and others.

	Effects on others		
	Beneficial	Neutral	Harmful
Effects on target(s)			
Beneficial	Benign	Proprietary	Inconsiderate
Harmful	Predatory	Punitive	Destructive

neutral to others (Fraser and Dando 2001). Finally, "destructive" applications may be harmful to both targets and others, like, for example, the development of genetically edited organisms for bioterrorism, whose impact may propagate in an incontrollable way (Ahteensuu 2017).

Different regulatory tools can help stimulate positive externalities or contain negative ones. The unconditional ban of genome editing would be only appropriate for those applications which have destructive effects (i.e. the bottom right cell in Table 2), while permissive regulations would just help the development of benign applications (i.e. the top left cell in Table 2). Nodality tools (e.g. monitoring genome editing activity and public engagement) can help increase awareness of externality effects, but also take the form of investigative or intelligence activities that may be required in order to detect the development of inconsiderate and destructive applications (i.e. the right-end cells in Table 2). Authority tools (e.g. a regime of licenses and permits) seem especially helpful to prevent the development of applications that have intended harmful effects on targets or possible harmful externalities (i.e. the bottom and right-end cells in Table 2). Treasure tools (e.g. scholarship and research funding) may be used to stimulate the development of benign or proprietary applications (i.e. the top and top-left cells in Table 2). Organization tools (e.g. government labs) seem advantageous in every respect, including the possibility for a government to play a direct role in the development of advantageous applications and in the acquisition of knowledge about possible harmful effects or side-effects of genome editing. Harmful applications of genome editing may be developed by other country governments or terrorist organizations, which would make a government a laggard in the technology race and therefore less capable to cope with related sources of threats (e.g. in the development of vaccines to bioweapons).

Regulations of genome editing are also affected by uncertainty concerning CRISPR applications. Uncertainty about the effects of genome editing abounds. Many variants in genes have no known functions or are of uncertain or unknown significance (Williams et al. 2021). It is uncertain whether scientists can actually achieve the desired genetic manipulation with enough precision (Guttinger 2018). There may be off-target events with unintended consequences (Baltimore et al. 2015). These sources of uncertainty pose issues to policy designers about whether applications have beneficial or harmful effects on targets and beneficial or harmful externalities onto individuals and the environment.

Knowledge about whether a genome editing application has beneficial, neutral or harmful effects may be incomplete or inaccurate. This uncertainty prevents to specify the extent to which a genetically edited application is welcome and may trigger adversarial attitudes because of the exposure to risk of harmful effects. If risk aversion is assumed, uncertainty results in a tendency to design policies that limit the use of genome editing. Extreme precautionary attitudes induce a preference toward restrictive regulations of activities and products whose externalities are not fully understood, in addition to the inclination toward restrictive regulations that arise from uncertainty on the effects of genome editing applications on the very targets. The 2018 ruling of the ECJ, for example, extended the application of precautionary policies that had been

originally adopted toward the commercialization of GMOs to genome edited products, irrespective of the innovative features of genome editing as a form of genetic manipulation (Callway 2018; Kupferschmidt 2018).

5. Discussion

The presence of externalities and uncertainty in CRISPR applications helps clarify the role of multiple tools that countries adopt to regulate genome editing. The selection of a mix of regulatory tools is intended to stimulate the development of genome editing applications while also to contain or mitigate their possible unwelcome effects. In a temporal perspective, a mix of regulatory tools provides a way to let technology and applications of genome editing develop while policy-makers learn which applications deliver beneficial effects and which ones call for more stringent approaches. The design of regulatory policies for genome editing should take advantage from a deliberate learning strategy, which could be pursued along the following lines.

First, policy-makers should attain the reduction of uncertainty concerning the effects of genome editing on the targets and externalities onto individuals and the environment. Various regulatory tools can help increase knowledge about the direct and externality effects of genome editing applications. For example, private operators may be required to disclose genome editing activity and research findings, licenses or permits may be required before undertaking genome editing research or commercialization of genome edited products, publicly funded research activity may be subjected to detailed reporting requirements and government labs may directly contribute learning about the effects of genome editing manipulations. A challenge for policy-makers would be to strike a balance between uncertainty reduction and excessive intrusion into private research and business activity, which might overburden private operators and researchers with red tape, discourage innovation and – in an international perspective – make domestic development of genome editing disadvantaged with respect to countries with more permissive regulations.

Second, policy-makers should diversify regulatory tools depending on existing knowledge about possible harmful effects or side-effects of genome editing applications. Rather than a "one size fits all" regime, specific regulatory tools should be used depending on the state-of-the-art of scientific knowledge about particular areas of genome editing applications. As uncertainty is reduced and externalities are better understood, regulatory tools may become more permissive. This approach would require some flexibility and discretion granted to regulatory authorities, and the update of regulatory institutions and practices over time. Challenges for policy-makers would be the one to allocate responsibility for the selection of regulatory tools and to which particular areas, the one to choose the timing of regulatory relaxation, and the one to coordinate the selection of regulatory tools with other countries, especially main international trade partners.

Third, policy-makers should be attentive to communicate scientific findings on genome editing to the public (Burall 2018). Science communication poses general issues of credibility, persuasion, and trust (Fischhoff and Scheufele 2013; Weingart and Guenther 2016). Communication of genome editing bears the risk that narratives are

framed or interpreted in ways that distort perceptions of the benefits and harms of genome editing applications. In a possible scenario, confusion between genome edited products and genetically modified products may trigger adverse attitudes and make the public incline to extend restrictive regulations to genome editing applications. In another possible scenario, the risk of harmful externalities may be discounted because of an optimism bias (Costa-Font, Mossialos, and Rudisill 2009). A challenge for policy-makers would be the one to engage the public in a way that regulatory policy preferences develop over time while avoiding abrupt swings between over-cautionary and overly permissive views.

6. Conclusions

The design of regulatory policies for genome editing is highly controversial and still unsettled. Issues arise because of the diverse effects of genome editing applications, on both targets and other individuals, species and the environment. The presence of externalities, in particular, entails that genome editing applications can have side-effects that regulations should consider. Uncertainty about the effects of genome editing applications, moreover, calls for further research to clarify whether regulatory policies should stimulate the development of genome editing or contain or mitigate harmful consequences of genetically edited products.

This study illustrates the advantages of mapping out externalities and uncertainty around genome editing. The identification of externalities and the appraisal of uncertainty help select regulatory tools depending on the beneficial, neutral and harmful side-effects that arise from genome editing products. Learning about the effects of genome editing is crucial for policy-makers in order to fine-tune regulations to particular areas of genome editing applications, while also taking into account other countries' regulatory policies. Overly restrictive regulatory policies may hinder innovation and, relatedly, country competitiveness. Excessively permissive regulations, instead, may result in blame attributions, legal disputes and erosion of public trust toward science and technology.

It seems especially important to remark, lastly, that regulation of genome editing is sensitive to the international context. Advances in genome editing can potentially revolutionize the trio of red, green and white biotechnologies (i.e. biomedicine, plant breeding and industrial, Tylecote 2019). Countries that lag behind in the technology race may find themselves losing competitiveness with respect to those that provide more advantageous conditions for research and development of applications. Countries that are at the forefront of genome editing science and technology may surpass others on the geopolitical, military and international trade domains. The design of regulations of genome editing should consider options for coordinated regulatory tools and collaborative strategies across countries such as, for example, exchange of information on genome editing activity in a way akin to other policy domains (e.g. global tax cooperation).

This study presents limitations that arise from the narrow focus on the role of externalities and uncertainty on policy design. Policy design of genome editing can be affected by other factors, such as, for example, ethical considerations and conditions

that arise from the pursue of industrial, health and environmental policy goals. Furthermore, policy design choices may also take into consideration situational factors, like, for example, conditions that arise from competition for talents in the international arena. Further research could extend attention to other factors in the design of regulation of genome editing and explore the role of externalities and uncertainty in policy design in the regulation of other emerging technologies.

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