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Snipping around for food: Economic, ethical and policy implications of CRISPR/Cas genome editing

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Abstract

CRISPR/Cas genome editing has the potential to revolutionise agricultural biotechnology and breeding. Also, it can contribute to advancing modern agriculture in multiple respects and lead to shifts in market structure. However, genetic engineering is a highly contested and controversial societal issue. Thus, CRISPR/Cas poses new questions regarding preferences of consumers and producers, food ethics and governance. Precision, easiness-to-use and low costs of CRISPR/Cas make it a viable alternative to conventional breeding. Yet, nature-identical GMOs blur the boundary between nature and technology and result in non-traceability of modifications, which calls for a rethinking of regulatory approaches. Finally, the speed with which the technology advances contrasts with the pace of related societal debates and regulatory processes.

Keywords: agricultural policy; bioethics; biotechnology; food production; genome editing; governance

1 Introduction

Recently, the US Department of Agriculture decided that a genome-edited non-browning mushroom (*Agaricus bisporus*) is not subject to conventional regulation of genetically modified (GM) crops, as it was created by 'knocking out' a gene responsible for browning by means of the CRISPR/Cas system without leaving traces of genetic engineering (Waltz, 2016). The mushroom can be considered an example of a nature-identical GM[1] product, the change in the fungus' phenotype being in principle indistinguishable from the result of conventional breeding or natural mutation. Meanwhile, in the EU, the European Court of Justice is supposed to decide whether *targeted mutagenesis*, i.e. the targeted modification of small parts of a plant's or animal's DNA by means of CRISPR/Cas or another genome editing technique falls under the conventional GM regulation.

Those are two examples for already ongoing political processes triggered by the advent of CRISPR/Cas genome editing, a novel and highly potent genetic engineering technique, developed in 2012 (Jinek et al., 2012). This new technique combines a number of characteristics which significantly enlarge the option space of biotechnology in general and agricultural biotech in particular: it is highly precise, flexible, cheap and relatively easy in application. Thus, it is supposed to have a significant potential for future agricultural development (Paul and Qi, 2016; Zilberman et al., 2018a).

CRISPR/Cas opens up new possibilities for the future of breeding and therefore for the entire agricultural sector. Already, the CRISPR/Cas system was successfully applied for genome editing in a range of agricultural plants such as soybean (Jacobs et al., 2015; Z. Li et al., 2015), maize (Svitashev et al., 2015), tobacco, sorghum, rice (Woo et al., 2015) and tomato (Brooks et al., 2014). There are studies with direct potential for application to livestock

[1] For explanations of terms from biotechnology and genetics, consult the glossary in the Appendix.

breeding, for example in goats (Ni et al., 2014) and sheep (Han et al., 2014). In addition, there is a broad range of studies demonstrating the feasibility of CRISPR/Cas genome editing in breeding of key livestock species, although to date they have mainly aimed at biomedical applications using animals as model species, including pigs (P. Li et al., 2015), chicken (Véron et al., 2015) and rabbits (Honda et al., 2015).

At the same time, green biotechnology remains controversial and heavily regulated, even though it has been argued that it has the potential to contribute to a more sustainable agriculture (Bartkowski, 2017; Ronald and Adamchak, 2008; taz, 2016). CRISPR/Cas genome editing has significant potential in this context, but it also creates novel challenges that involve known and unknown risks.

Surprisingly, even though CRISPR/Cas genome editing has stirred up a huge literature since its invention in 2012, there are hardly any broad analyses of the potentials and challenges it poses in the context of food production from a social science point of view. A few specific proposals for CRISPR/Cas-sensitive regulatory reform have been made in recent literature (e.g. Huang et al., 2016; Ishii and Araki, 2016); also, GM labelling has been discussed in the context of genome editing (McCluskey et al., 2018; Zilberman et al., 2018b). There is, however, a lack of a broader consideration of relevant ethical, economic and governance issues. In this paper, we provide a broad social science perspective on the implications of CRISPR/Cas genome editing for agriculture, which we take here as an entry point, and offer a conceptual view on socio-ecological-technical determinants relevant for CRIPSR/Cas-specific regulations. We demonstrate that unique traits of the technology and its products become interwoven with new perceptions, new ethical considerations and new representations of the nature–technology boundary which then feedback on how society handles and implements this technology. To analyse these entangled society–technology processes we build upon existing literature on GM food and related literatures from economics, ethics and policy

analysis. We use the insights generated in this literature as an analytical frame to dissect the societal implications of CRISPR/Cas and its unique characteristics in a breeding context. Those unique characteristics are derived from a critical reading of publications on CRISPR/Cas from other disciplines, such as biotechnology, plant genetics and agricultural sciences.

CRISPR/Cas genome editing is already a well-developed technique that develops at an accelerating pace; furthermore, while no genome-edited products have yet reached the market, the political debates surrounding the technique suggest that this may be only a matter of time. Meanwhile, societal debate about the desirability of genome editing (as compared to conventional GM techniques) has so far been limited. Therefore, our analysis takes the availability of the technology as given and focuses on its possible consequences for society in general and for agricultural governance in particular. However, we acknowledge that we are looking at a complex social–technical system, in which relationships between the various components (society, politics, technology, markets, nature) are not unidirectional, but rather involve feedback loops and can be legitimately analysed from different entry points.

The paper is structured as follows: in Section 2 the CRISPR/Cas genome editing technology is introduced, including its origin, basic genetic mechanisms and novel aspects. Section 3 compares CRISPR/Cas with previous GM techniques in the context of agriculture; it lays focus on the technology's potential to reduce entry barriers in biotech markets (3.1) and on its potential in inducing non-transgenic modifications (3.2). Section 4 focuses on the socio-economic challenges posed by CRISPR/Cas genome editing for agriculture in general and for agricultural governance in particular. We consider the likely influence of CRISPR/Cas on the preferences of consumers and producers (4.1) as well as its ethical implications (4.2). As the CRISPR/Cas-specific research in these areas is scarce, we build upon insights from related literatures by informed systematic analysis. Section 4.3 combines the previously discussed

threads and derives implications for regulatory governance regimes. Section 5 concludes and suggests adaptation of current regulations to the specificities of the discussed technology.

2 CRISPR/Cas: from a natural immune system to genome editing

A range of different GM technologies are referred to as genome editing (Nagamangala Kanchiswamy et al., 2015). Among them, CRISPR/Cas is closest to fulfilling the promises of the editing metaphor: changing genetic code as easily as editing a digital text document.

While nowadays CRISPR/Cas is mostly associated with biotechnology, it is actually based on a mechanism naturally occurring in bacterial cells. Initially, Mojica et al. (2005) hypothesised that clustered regularly interspaced short palindromic repeats (CRISPR) sequences provide bacteria with an immune defence against viral attacks. Shortly after that, an experimental study verified that CRISPR sequences interact with Cas (CRISPR-associated) enzymes to constitute an essential part of the immune system in bacteria (Barrangou et al., 2007): if a bacterium survives the first attack of a virus, the cell integrates parts of the viral DNA in its own genome in the CRISPR sequence. The next time the virus infects the cell an RNA copy is made of the viral DNA, which serves as a targeting mechanism. The RNA copy binds to the Cas9 enzyme and recognizes the DNA of the virus by base-pairing, ‘guiding’ the enzyme, which then cuts the viral DNA at a specific sequence and thus neutralises the virus. This precise and highly adaptive bacterial immune system is the natural foundation of the CRISPR/Cas technology.

In their seminal paper Jinek et al. (2012) presented a new genome editing tool based on the natural CRISPR/Cas system.[2] They found that two RNAs (crRNA and tracrRNA) are required to guide the Cas9 enzyme to the target sequence and simplified the natural mechanism by fusing them into a single guide RNA. Their study delivered a GM technology that combines the strength of enzymes as precise gene-scissors and the strength of RNA as precise targeting mechanism for specific DNA sequences that can be easily synthesized in the lab to target particular genes.

CRISPR/Cas is not the only genome editing tool enabling precise alterations of DNA. However, earlier genome editing technologies combine the gene scissor and the targeting function in just one protein molecule. Therefore, for every gene one wishes to edit a new protein has to be engineered, so as to adapt the targeting part of the protein to the gene sequence. Engineering proteins is time-consuming and costly due to their complex chemical structure. Therefore, a profitable application of these technologies has proven difficult. The CRISPR/Cas tool separates the scissor function (protein) and the targeting function (RNA). Only the RNA needs to be modified for each new application. Because RNAs are much easier to engineer in the laboratory, this results in a much more efficient process. All that the CRISPR/Cas system has to do is cut the DNA at a specified location – depending on where it cuts and whether some foreign DNA has been introduced into the cell, the cell's own repair mechanisms lead to the desired change.

A novel aspect of CRISPR/Cas is that it makes so-called *multiplexing* (Cong et al., 2013) much easier as compared with other GM techniques: multiple guide RNAs, targeting different DNA sequences, can be introduced into a cell together with the Cas9 protein at once. Thus, multiple modifications can be made at the same time. Since plant genomes are often

[2] For more details about the history of the relevant discoveries and also about the controversial attribution of scientific credits we refer the reader to Lander (2016) and Ledford (2016).

polyploid, i.e. carrying multiple gene copies, genetic engineering of a single trait (i.e. characteristic of the organism) requires editing multiple DNA sequences. A common example is hexaploid wheat, carrying six copies of each gene. Therefore, multiplexing can be particularly useful for plant breeding (Khlestkina and Shumny, 2016).

While CRISPR/Cas does nothing, on the molecular level, that could not be done before, its efficiency and simplicity have profound consequences for what can be done to breed new crop plants and livestock varieties.

3 Potential impacts of CRISPR/Cas on future of crop and livestock breeding

There already exists a large economic and social science literature on various aspects of genetic engineering in general and GM crops in particular (Brookes and Barfoot, 2012; Dannenberg, 2009; Gaisford et al., 2001; Gregorowius et al., 2012; Just et al., 2006; Lusk et al., 2005; Qaim, 2009; Zilberman et al., 2018a). However, an analysis of the specific implications of CRISPR/Cas genome editing for livestock and crop plant breeding is still missing, even more one with a socio-economic perspective integrating ethical and governance aspects.

There are two main issues related to CRISPR/Cas genome editing that appear relevant. As mentioned above, in comparison to conventional GM techniques and, to some extent, also conventional breeding techniques, CRISPR/Cas is cheap and easy-to-use, while being highly precise and very potent (allowing for multiple genetic modifications at once) at the same time. These characteristics result in a potential to significantly reduce entry barriers in biotech markets. Furthermore, CRISPR/Cas accelerates breeding and can be a viable alternative to conventional breeding approaches.

The two-step literature review which we conducted to substantiate our socio-economic and governance perspectives and arguments on this topic, followed qualitative social science methods. After having derived the specificities introduced above, we structured reviewed texts accordingly: low-cost, fast spread, easy-to-use, highly precise, nature-identical GMO. Those turned out to be the most relevant characteristics in the CRISPR/Cas technology when considering its governance and ethical challenges.

After having substantiated these specificities by a review of mainly natural science literature, we discussed the ethical, economic and political considerations, based on the interdisciplinary perspectives of the authors' team. The additional value of this contribution is thus the combination of these perspectives and enriching the current widespread monodisciplinary research related to CRISPR/Cas. We extracted topics and constructed categories with implications for agriculture and its regulation, food preferences and governance (Bryman, 2016, p. 563). We based our qualitative content analysis (Mayring, 2014) on the following categories: reducing entry barriers, market diversification, non-traceability of modifications, decentralisation of knowledge, uncertainty about off-target alterations, deeply held values of stakeholders and moral attitudes of citizens. In this second round of literature review, we mainly analysed social science literature dealing with biotechnology and, where available, CRISPR/Cas.

3.1 Access to technology and implications for biotech markets

If the costs imposed by regulation upon every entity wishing to engage in genetic engineering are not taken into account, CRISPR/Cas genome editing can be viewed as having the potential to diversify the market for biotechnology by reducing market entry barriers. Before the advent of CRISPR/Cas, genetic engineering was an enterprise with very high upfront investment costs (including the costs of know-how, technical equipment and high opportunity costs of

time invested in each innovation), which partly explains the highly concentrated market structure of biotech industries. Now, the technique can arguably be applied at very low cost also by small biotech firms, non-profit organisations or public institutions.[3] Moreover, there seems to be a widespread practice of open access to information about this method, such as freeware computer programmes for designing guide RNAs (Khlestkina and Shumny, 2016). Of course, because its application requires profound knowledge about genetics and biotechnology, it is unlikely that it could be used by individual farmers. But it is definitely not necessary anymore to have the capital of multinational biotech companies to engage in genetic engineering, as CRISPR/Cas tools come at a fraction of the cost of other techniques (Ledford, 2015).

A consequence of this could be a significant change in the market structure of biotech industries (Brinegar et al., 2017). As of now, this is a highly concentrated market (Howard, 2015), as highlighted by the recent merger of Bayer and Monsanto. The above-mentioned market diversification potential of CRISPR/Cas genome editing might lead to a deconsolidation of the market, since big players would lose some of their comparative advantage in terms of scale effects and capital availability. This could have significant repercussions, especially a refocus regarding the goals of GM breeding (on this, see below).

3.2 Acceleration of breeding, cisgenesis and nature-identical modifications

Before the advent of CRISPR/Cas, genetic engineering has been mostly used to introduce traits which cannot be introduced by means of conventional breeding, for instance by transferring a gene from bacteria (*Bacillus thuringiensis*) to maize to produce insect-resistant

[3] Note that there is an ongoing legal dispute surrounding CRISPR/Cas-related patents; it is therefore currently not clear how freely the technology can be used (Contreras and Sherkow, 2017a, 2017b; Horn, 2017; McGuire, 2016).

maize varieties (so-called Bt corn). Even though conventional crossbreeding and selection, applied to breed within species boundaries, can take up to a decade (Becker, 2011) and requires considerable financial investments, the capital requirements and know-how needed for genetic engineering meant that it was not a viable alternative for conventional breeding. With the advent of CRISPR/Cas genome editing, this has changed: genetic engineering has become an economically viable alternative to conventional breeding, also within species boundaries, at least for those species whose genomes are sufficiently well-understood. Instead of complex cross-breeding and back-crossing schemes between oftentimes multiple different varieties, genes can now be edited without the need of any biophysical exchange between different varieties. Therefore, CRISPR/Cas has the potential to considerably speed up the breeding of crop plants (Belhaj et al., 2015) and livestock (Laible et al., 2015).

A particularly interesting application of cisgenesis, i.e. the introduction of genes from related organisms by means of genetic engineering, that might be spurred by CRISPR/Cas genome editing is the so-called 'rewilding' (Palmgren et al., 2015) – the 're-introduction' of properties that were lost in the course of breeding for human purposes. Therefore, CRISPR/Cas opens the possibility to tap into the potential of vast genetic resources residing in wild relatives and old landraces of important crop plants and livestock. A similar application is the silencing or knocking out (removing) of 'undesirable' genes. Recent applications include the already mentioned non-browning mushrooms or virus-resistant cucumber (Chandrasekaran et al., 2016).

A rather fundamental consequence of the CRISPR/Cas technology is that it opens up the possibility of creating nature-identical genetically modified organisms (nGMOs). These are new crop or livestock varieties created via non-transgenic modification without leaving traces of genetic engineering (especially foreign DNA fragments) in the resulting organism. An nGMO could theoretically also be the outcome of natural evolution or conventional breeding.

Note, though, that the possibility of completely non-traceable modifications has been questioned (Kim and Kim, 2016). Also, there are multiple other genome-editing technologies that can be used to breed nGMOs and not all GMOs created with the help of CRISPR/Cas are nature-identical. Nonetheless, CRISPR/Cas has quickly become, for reasons outlined above, the most widespread genome-editing technique (Brinegar et al., 2017).

The advent of nGMOs through genome editing technology blurs the boundary between nature and technology with significant implications for agriculture and its regulation. For the first time genetic engineering has become a serious alternative to conventional breeding within species boundaries.

4 Socio-economic implications of CRISPR/Cas: preferences, ethics and governance

CRISPR/Cas is likely to have profound socio-economic consequences in the area of agricultural biotechnology as well as, generally, crop plant and livestock breeding. Especially, its emergence is believed to pose a significant challenge for current GM regulatory frameworks, particularly in the EU (Wolt et al., 2016). It is very likely that due to CRISPR/Cas applications these frameworks will have to be reformed – in fact, concrete proposals in this regard have already been made (e.g. Araki and Ishii, 2015; Huang et al., 2016; Ishii and Araki, 2016). The approach of this paper is to discuss factors that should be taken into account when devising new, CRISPR/Cas-sensitive governance structures, without proposing specific changes to current regulations.

Biotech regulations, particularly agricultural GM regulations, have always been subject to debates. Various governance options can either facilitate or hamper the spread of GM technologies and, thus, impact on the agricultural sector. In the field of GM technology, the

debate is often ideologically motivated and highlights a high uncertainty about future risks and challenges (Hielscher et al., 2016), which both require elaborate negotiation processes; the transaction costs of negotiation among the involved parties with heterogeneous positions towards the technology are very high. Further, in the absence of scientifically clear predictions, various uncertainties apply to the CRISPR/Cas technology, including the so-called known- and the unknown-unknowns. The former represent the expected or foreseeable states of the world in the future and the latter those which cannot be anticipated on the basis of past experience or investigation (Kundzewicz et al., 2018). Unknown unknowns pose particular governance and communicating challenges.

Three subsequently described factors should be taken into account when devising and deliberating a corresponding GM regulatory framework (cf. Hagedorn, 2008). First, the *preferences* of the relevant stakeholder groups should be taken into account, particularly (potential) consumers and producers of GM products. Second, *ethical issues* related to CRISPR/Cas applications in the context of agricultural production are an important factor. Third, more generally and building upon this, CRISPR/Cas-related transactions exhibit a number of specific *characteristics* which are relevant for the efficacy and efficiency of different governance approaches. In other words, it is important to take into account *what we (as society) want, what we should* and *what we can*.

To date, voices in the debate about the need to rethink regulation in the wake of the emergence of CRISPR/Cas mostly focused on one of the three aspects mentioned. Some emphasise the need to involve stakeholders and honour their preferences (Jasanoff et al., 2015; Kuzma, 2016; Malyska et al., 2016); others reject reservations of stakeholders as irrational and call for a more ‘scientifically’ informed approach (Huang et al., 2016; Pollock, 2016); in some contexts, ethical considerations have been argued to be decisive (Baumann,

2016). We argue here that in designing a governance structure that is adapted to the specificities of CRISPR/Cas, all these aspects should be taken into account.

4.1 Influence of CRISPR/Cas on preferences of consumers and producers

There are two reasons why especially preferences of consumers (but also producers) of agricultural products are a crucial factor to be considered when designing well-adapted governance structures for the new GM technology: first, there are general ethical arguments in favour of including stakeholders in decisions that involve their deeply held values (Jasanoff et al., 2015); second, from a pragmatic point of view, ignoring consumer preferences might render regulation irrelevant, leading to implicit or explicit boycotts of GM products: 'the key issue is not whether new crop varieties are as safe as those developed by conventional plant breeding and thus fall outside the scope of current GMO legislation, but whether society perceives them as such' (Malyska et al., 2016, p. 532; see also Kuzma, 2016; Lofstedt, 2013). However, the analysis of preferences for and against GM crops is challenging as it is a highly value-laden and controversial topic (Hess et al., 2016; Hielscher et al., 2016; Vigani and Olper, 2013). Nonetheless, CRISPR/Cas differs from current GM technologies in ways which might cause a shift in the perception of agricultural biotechnology.

The empirical literature inquiring into consumers' preferences for and acceptance of GM products (Costa-Font et al., 2008; Dannenberg, 2009; Hess et al., 2016; Huffman and Rousu, 2006; Lusk et al., 2005) focuses frequently on the influence of consumer characteristics on acceptance or willingness-to-pay (WTP) for GM rather than on the characteristics of the products themselves; even those focusing on product characteristics are not necessarily applicable to CRISPR/Cas because the most relevant characteristics are novel and specific to this technique (see section 3). Two interesting recent contributions in this context are

Delwaide et al.'s (2015) and Edenbrandt et al.'s (2018) investigations of the difference in consumer acceptance between transgenesis and cisgenesis. Combined with the insight that CRISPR/Cas facilitates a shift away from transgenesis (see section 3.2), their results suggest that the new technique might alleviate some reluctance of consumers towards GMOs. Furthermore, since 'naturalness' is an important point of reference for moral judgements and thus acceptance (see also next section), nGMOs might especially change the attitude of consumers towards genetic engineering of crop plants and livestock. But the difference between transgenesis and cisgenesis is only one issue which requires attention. The usual crude differentiation between GM and non-GM crops in acceptance/WTP studies obscures the entanglement of multiple considerations on the side of the participants. For instance, genetic engineering is commonly associated with industrial agriculture (e.g. Gomiero, 2017) – if it would be combined with other cultivation practices, acceptance might change. In fact, Urs Niggli, an influential Swiss plant scientist and critic of conventional agriculture, recently called upon the organic farming community to rethink their strict rejection of genetic engineering and argued in favour of harnessing the potential of CRISPR/Cas genome editing for organic agriculture (taz, 2016). More generally, there is a need to differentiate between multiple factors that influence acceptance of agricultural technologies, including genetic engineering:

- breeding techniques, for example conventional breeding, mutagenesis, transgenesis, cisgenesis;
- breeding goals, for example herbicide resistance, increase in nutritional content, resistance to extreme weather events;
- cultivation methods, for example industrial monoculture, small-scale conventional, organic.

The latter two points can also be summarised as *(perceived) compatibility with various kinds of agriculture*, especially along the dimensions large-scale vs. small-scale and conventional vs. organic. GM food is often viewed critically because of its historic entanglement with industrial agriculture (Gomiero, 2017; Marsden, 2008). Furthermore, since the multinational corporations involved in agricultural biotechnology are viewed critically by many consumers (Agence France-Presse, 2015) and consumer opinion about GMO is heavily entangled with the identification of biotechnology with these multinationals, the market diversification potential of CRISPR/Cas could have significant influence on the acceptance of GM products.

Lusk et al. (2014, p. 652) point out that 'many in the agricultural production community bemoan the public's lack of understanding of commercial agriculture and argue for more "science based" regulation. Although agricultural producer groups differ widely from the average food consumer in their beliefs about the safety and quality of GM foods [...] it is clear that an understanding of these controversies, not to mention the impacts of public policies, requires a better understanding of producer and consumer beliefs.' The new possibilities offered by CRISPR/Cas offer an opportunity for a new dialogue between producers, consumers and regulators, which can lead to aligning subjective beliefs with facts, but also the insight that the uncertainties and normative issues surrounding biotechnology (see also next section) mean that a purely 'science-based regulatory approach' may well be elusive (Kettenburg et al., 2018). Furthermore, as shown by Edenbrandt and Smed (2018), consumer preferences are only a limited predictor of political preferences – so a focus on consumer preferences, let alone actual purchases, is not sufficient for informing agricultural governance.

Acceptance of GMOs by producers is another relevant issue in the context of CRISPR/Cas governance. Here, too, we assume that CRISPR/Cas can have numerous repercussions. First, the choice between conventionally bred varieties and GM crops is obviously dependent on the acceptance of the resulting agricultural products by consumers – if CRISPR/Cas would

decrease the reluctance of consumers towards GMOs (as hypothesised above), adopting GM crops would be less risky for farmers. Second, changes in market structure that might be caused by CRISPR/Cas (see section 3.1) could be beneficial for those farmers who are willing to adopt GM crops but up to now have been faced by the considerable market power of biotech multinationals and their ability to impose restrictions upon the farmers' activities that are related to the use of the GM crops. For instance, Qaim and de Janvry (2003) showed that corporate monopoly power restricted adoption of Bt cotton by Argentinian farmers. Third, the likely turn towards cisgenesis and gene silencing can be expected to steer agricultural biotechnology towards so-called second generation GM crops, i.e. such that exhibit increased tolerance to environmental stresses (Abdelrahman et al., 2018), which might be of more interest than conventional GM crops to farmers especially in areas facing land degradation and increasing frequencies or severity of extreme weather events due to climate change. As there is little available research on these topics, however, our insights regarding producers' preferences are hypotheses that remain to be tested.

4.2 CRISPR/Cas-related ethical issues

Turning from the perspectives of individual consumers and producers to society at large, the development and application of any new technology like CRISPR/Cas raises moral questions as it affects the living conditions of current or future moral entities, including the non-human environment. New technologies allow performing new actions and thus pose the questions about the morality of an action in a new way. This is what Verbeek (2006) and Inghelbrecht et al. (2017) call co-shaping or co-evolvement of technology and ethical concerns. However, the fundamental ethical theories as a source of reasoning about what is morally right or wrong remain the same. New technologies can be viewed as special cases for moral reasoning. Constitutive for value-pluralist societies is the juxtaposition of several often competing moral

arguments that are rooted in different ethical theories (Ott, 2014). Thus ethics does not give a single answer to the moral questions that arise due to a new technology.

In general the public debate on GM crops in agriculture is dominated characterised by consequentialist and deontological perspective. The most common consequentialist ethics is act-utilitarianism with its focus on the consequences of an action. It develops a pre-moral value that is happiness or utility. Morally right are those actions that maximise the utility of the greatest number (Frankena, 1963). In contrast to this, deontology focuses on the rightness of an action as such and its compliance with certain principles that are generally accepted by the society (Frankena, 1963). If we assume that the development of a new technology reframes the moral debate, the question arises how CRISPR/Cas has changed or will change the moral discourse on genetic engineering as compared to the former GM debate.

The consequentialist perspective usually focuses on the risks and benefits of certain innovations for human beings. The GM debate was dominated by reflection about the risks and benefits of a technology that is able to overstep species barriers (Carpenter, 2010; Klümper and Qaim, 2014).

Although CRISPR/Cas allows for both transgenesis and cisgenesis, the current debate on the acceptability in agriculture mainly focuses on cisgenic products (Palmgren et al., 2015; Schouten et al., 2006). From this scientific perspective the technology as such is morally neutral (Weigel, 2017). For nGMOs, risks of the new plants or animals are similar to the conventionally bred counterparts as they could be the result of natural evolution (Zilberman et al., 2018a). Although some critics of the new technique warn against unintended risks of off-target mutations as well as the possibility of misuse (Steinbrecher, 2015), the main argument for the rejection of genetic engineering, i.e. the risks to the environment and human health due to breaking reproductive barriers, seems now obsolete. Therefore, we can conclude that from

a utilitarian perspective the application of CRISPR/Cas is less risky than the former GM technique and is thus more morally acceptable. Nevertheless, one has to keep in mind that an ethical assessment is more than pure risk assessment and must include the effect the modification will have on the entity with regard to pain or suffering. Furthermore, the risk perception (additive or cumulative) and the time horizon considered influence the concrete results.

While the consequentalist perspective, often in its narrow interpretation as risk assessment, dominates the debate in natural science, the public discourse is dominated by deontological considerations (Kettenburg et al., 2018). As a normative point of reference for judging the rightness of an action one finds 'naturalness' as a moral concept (Gregorowius et al., 2012; van Haperen et al., 2012; Verhoog, 2003). Although the term naturalness is not homogeneously used, all interpretations have in common that naturalness is understood as a normative argument. It implies that nature and its order is per se good and can serve as a point of reference for evaluating changes both at individual and system levels, even if the perspective has to accept the criticism of conducting a naturalistic fallacy, i.e. the deduction of a value statement from facts about nature.

With regard to CRISPR/Cas, naturalness as a normative argument is applied to both the product, the result and the process of breeding itself. These perspectives correspond with different understandings of naturalness, which Siipi (2008) calls the history-based and property-based naturalness. While property-based naturalness looks at the current properties of an entity disregarding the manner in which they appeared, history-based naturalness emphasizes the origin of an entity.

That means that from a property based perspective the application of a highly artificial technology like CRISPR/Cas end-products can be viewed as natural, if it is similar to a

product that could have developed by nature. Looking on the process of breeding, there are two opposing understandings of naturalness. In one concept, nature is seen as a long and complex evolutionary process that has developed over time and cannot be simulated by humans (Reiss and Straughan, 1996): Central aspects of the complex system are not well understood by humans despite all scientific efforts. Here nature is viewed as a safety mechanism that will especially become important when humans' assumptions about the interaction within an ecosystem or on the cell level prove to be false (Gregorowius et al., 2012; Karafyllis, 2003). According to this understanding, 'nature knows best' and therefore has an intrinsic value that should be respected. The more target-oriented and purposeful a technique is and the more it intrudes into the gene pool of a crop or an animal, the less morally acceptable it is because the safety mechanisms of nature will be disturbed (Reiss and Straughan, 1996). According to this understanding CRISPR/Cas has to be viewed as unnatural and therefore immoral.

Another concept is a more science-based understanding of naturalness. Here it is either argued that biotechnology is only mimicking natural processes and is therefore not more or less natural than nature itself or that breeding since the Neolithic revolution has not been natural because it has tried to adapt plants to human needs (Church and Regis, 2012; Zwart, 2009).

From this perspective CRISPR/Cas can be viewed as natural because the process of gene transfer in the lab is similar to a biological mechanism that has been discovered, not developed. These diverging interpretations of naturalness explain why 'naturalness' as an important argument in public debates is used by both advocates and opponents of CRISPR/Cas (Bioland, 2016; KWS, 2015).

In addition to the discussion of consequences and principle-based acceptability of biotechnology, the ethical debate on CRISPR/Cas in breeding is embedded into a general

moral critique of modern agriculture and its social and ecological acceptability. Here, one can observe a severe societal discontent with recent developments in agricultural production that is not due to a lack of information or understanding of modern food production but a widespread unease, scepticism and distrust into private and public actors and the decision-making processes along the entire food chain (see previous section). These societal and ecological concerns include property rights to genetic resources, patents to genetically modified plants and animals, access to gene pools as well as questions of seed and food sovereignty, effects on biodiversity and the reversibility of decisions.

What we can conclude from the considerations above is that even if CRISPR/Cas within species boundaries it is not morally neutral as any technology is of moral significance. The ethical challenge posed by the introduction CRISPR/Cas genome editing goes well beyond questions of acceptable consequences and side-effects, and includes fundamental societal questions of fairness and intra- and intergenerational justice (Dabrock, 2009). However, in pluralist societies we need a societal discourse about the guiding values regarding the development and application of any new technology. Therefore, deliberation should be an integral part of research and technological development.

4.3 Characteristics of transactions and implications for governance

An international ban, temporary moratorium, regulation or laissez-faire offer four general approaches of governing a new technology. Yet, due to the comparatively low cost and thus fast spread of CRISPR/Cas, together with the heterogeneity of regional ethical considerations, a ban or a moratorium do not seem to be relevant options; conversely, laissez-faire creates situations in which risk might occur before ethical due diligence (Evitt et al., 2015). Therefore, regulation appears to be the relevant governance approach. However, it is believed

that current regulatory frameworks are not suitable for CRISPR/Cas genome editing (Wolt et al., 2016).

There are particularly four characteristics of CRISPR/Cas-related transactions that call for special attention when designing regulations: 1) non-traceability in the resultant organism, 2) the decentralisation of knowledge and use, 3) the uncertainty about off-target alterations, 4) the speed of breeding.

1) There is scientific consensus, that if we are not able to determine in a nature-identical product of CRISPR/Cas genome editing how it came into being, monitoring, and thus governing, from the end-product is impossible. Current GM regulations do not apply, as they largely depend on the existence of an exogenous DNA sequence in the resultant organism, which is not applicable to nature-identical CRISPR/Cas products. While it has been argued that CRISPR/Cas leaves small amounts of foreign DNA in the genome (Kim and Kim, 2016), conventional analytical methods used by inspection bodies (Ahmed, 2002; Kim and Kim, 2016), such as PCR (polymerase chain reaction), cannot detect such evidence. This led, for instance, to USDA's above-mentioned decision not to subject the non-browning mushrooms to GM regulation. Even if traceability is generally possible, it would require the application of new analytical methods. Assuming that modifications in nature-identical CRISPR/Cas products are non-traceable, process-based regulatory approaches are necessary. Process-based regulation is much more difficult to set up, especially given the expected diversification of the producer market (see also below). Thus, while the status of CRISPR/Cas products as GMOs is not yet settled (Araki et al., 2014), at least in the case of nature-identical CRISPR/Cas products, non-traceability effectively precludes product-based regulation that would allow critical consumers to distinguish between GM and non-GM products, such as labelling (Zilberman et al., 2018b). Nonetheless, some authors (e.g. Hartung and Schiemann, 2014; Huang et al., 2016) call to evaluate new plant breeding techniques only according to the new

traits and the resulting end-product rather than the techniques used, which would effectively amount to a laissez-faire approach towards the CRISPR/Cas technique. Here, we would like to raise the argument that given ethically inspired reservations towards genome-edited products (see previous section), such an approach appears deeply problematic in a democratic society.

2) As CRISPR/Cas genome editing is a dramatically easy-to-use and inexpensive method (Araki and Ishii, 2015; Baltimore et al., 2015), the rising role of non-profit organizations and public institutions in the application of GM technology is expected in the literature (Brinegar et al., 2017). A decentralized access structure would require new governance arrangements and new property rights regimes. Current biotechnology regulations are committed to strict protection of intellectual property rights of a small number of large multinational companies. CRISPR/Cas genome editing has the potential to 'open up' this field and add further complexity to the debates about 'patenting life' (Sherkow and Greely, 2015). More generally, because CRISPR/Cas is likely to result in a surge of innovations, including new varieties of crops and livestock, it will likely trigger a wave of new patents (Brinegar et al., 2017; Webber, 2014). A question, that needs further investigation in our view, is how such patents will be used if their holders are for example non-profit organizations.

Widespread use of CRISPR/Cas, including non-profit organisations and smaller firms, might also lead in our view to an increase in biotech-related risks, both because of the diversification of sources of genetic modifications and because of the relative inexperience of some of the actors involved. Even with CRISPR/Cas, genetic engineering is a demanding and complex enterprise, involving large risks and high levels of uncertainty. In contrast to the limited capacities of smaller actors, the current biotech market players have many years of experience in dealing with these issues. Also, centralised monitoring of their activities (e.g. by the EFSA) is easier when the number of actors is small. We assume the ability of smaller players to

handle even existing hazards to be smaller than in the case of experienced companies, posing new challenges for regulation.

In the context of human genome, Baltimore et al. (2015) supports our point here, by arguing that those countries with highly developed bioscience capacities usually have a correspondingly tight regulatory system. If the technology now easily spreads to too many other socio-political, jurisdictional contexts, an institutional mismatch might evolve with a high risk of not being prepared to respond to hazards and potential risks, neither with effective regulation nor the corresponding governance mechanisms. This leads back to the two governance principles, the precautionary principle and adaptive management, recognized as suitable by (Kundzewicz et al. 2018) to handle the level of uncertainty.

3) An interesting regulatory approach mentioned by Evitt et al. (2015) and originating in human genetics is the consideration of prohibiting the use of CRISPR/Cas in any project that lacks a validated reversal strategy as long as we are not sure if the benefits and opportunities would actually outweigh the cost and unknown risks of unforeseen complications.[4] Thereby we have to consider not only possible unintended consequences of the intended modifications, but also the possibility of off-target mutations (Baker, 2014; Baltimore et al., 2015). Araki and Ishii (2015) regard the latter as one of the 'most critical issues in the agricultural use of GE.' Yet authors such as Paul and Qi (2016) pretend that CRISPR/Cas has the potential, particularly in crop development, to ensure organisms largely free of off-target mutations. Unintended consequences of genetic modifications, such as horizontal transgene transfer, i.e. the naturally occurring transfer of the inserted gene sequences to neighbouring plants, could be reduced by CRISPR/Cas as well (Khlestkina and Shumny, 2016).

4 This approach has obvious similarity to the concept of quasi-option value from environmental economics (Arrow and Fisher, 1974; Fisher and Hanemann, 1990), which dictates restrain from irreversible changes in the face of uncertainty.

Concretely, to deal with the irreversibility of technologically induced natural processes: ex-ante regulation or ex-post liability have been suggested (Beckmann et al., 2006). Beckmann et al. (2006) discuss this for the coexistence rule in EU agriculture, according to which no form of agriculture should be generally excluded; we can draw parallels in the conceptual considerations to the case of regulating CRISPR/Cas technology. In the GM debate we face a similarly broad spectrum of ideas ranging from clear calls for a legal ban of the technology using ex-ante regulations, to undecided debates about the best measure to facilitate the adoption of that technology. A country that imposes less strict regulations on that technology and more innovative ex-post liability rules is more likely to gain experience with that technology. Questions to be answered in this context include according to Beckmann et al (2006): Who should bear the ex-post tort liability costs in case of off-target alterations? Who should bear the burden of proof? Can a farmer who is not cultivating GM bred varieties claim compensation for damages? From whom? Following Beckmann et al. (2006), we could also ask the question the other way around: can a farmer, a consumer or a patient claim compensation for foregone benefits for not being allowed to grow, buy or be treated with products/organisms based on the CRISPR/Cas technology?

4) Finally, other than conventional breeding, CRISPR/Cas genome editing does not require labour-intensive and time-consuming screens to identify the desired plant mutants (Baker, 2014; Belhaj et al., 2015). Further, CRISPR/Cas technology is undergoing a rapid evolution itself. Examples include new, more efficient enzymes to replace Cas9 (Burstein et al., 2017; Cox et al., 2017; Fonfara et al., 2016; Zetsche et al., 2015) and more precise systems for specific modification purposes (Gaudelli et al., 2017). We want to highlight that this characteristic – the speed of breeding – is extremely relevant for all that has been said above, as it puts the development of adjusted and flexible regulatory governance structures under a

time constraint. Otherwise, the technological development will overrun the required discursive processes of decision making.

Here, society faces a big trade-off between, on the one hand, fast-to-implement command-and-control ex-ante regulations and, on the other hand, ex-post liability rules based on societal agreement who should hold the initial property rights, which take long to be worked out but could be more effective in the long-run.

5 Conclusions

In this paper, we discussed the implications of a novel and considered-revolutionary GM technique, CRISPR/Cas genome editing, in the context of food production. We argued that its unique combination of precision, easiness-to-use, speed and low cost creates substantial opportunities and challenges for agricultural policy. We identified two particularly far-reaching implications of CRISPR/Cas genome editing, viz. that it has the potential to reduce entry barriers to biotechnology markets and that it can be expected to fuel a shift away from transgenesis and towards cisgenesis and gene silencing, also creating the new category of nature-identical GMOs, which blur the boundary between nature and technology. On the basis of these insights, we turned the focus on governance needs created by CRISPR/Cas. We argue that a regulatory framework concerning such controversial and consequential technology that will be effective and cost-efficient in the long-run has to take into account: preferences of consumers and producers, ethical considerations and characteristics of relevant transactions. Taking these factors into account, we emphasised a number of CRISPR/Cas-specific issues that any attempt to adapt current GM regulations to the specifics of this new technology should consider.

Our paper sheds light on a number of fundamental trade-offs to be considered in the context of CRISPR/Cas genome editing. If nature-identical GMOs are not traceable, their regulation, including patenting, cannot be based on the end-product if the principle of consumer sovereignty for GM-critical consumers is to be adhered to. If CRISPR/Cas offers a more widespread, even open-access use, it may lead to market diversification, but it likewise brings in new actors without experience in handling risks. If regulators need to act fast to keep up with the development, the time required for a thorough normative societal debate may not be available.

An important trade-off to be made is between strict regulation with considerable compliance costs and the widespread use of the technology with associated risks. A strict regulatory framework, particularly process regulation, would lead to a high cost share for companies to meet the various requirements. As a consequence, use of the new technology would most likely be limited to creation of highly profitable crops (Voytas and Gao, 2014). That would limit the benefits of providing a relatively easy-to-use technology, possibly in a partly open-access manner, also to actors who might be interested in increasing the agricultural productivity of minor crops, including crops that are interesting for organic farming or adapted to less favoured areas, or simply vegetables or horticultural species which lack high profit margins. Such actors might not be able to bear the considerable compliance costs of demanding governmental regulatory packages.

To alleviate these trade-offs, similarly to the situation in the biomedical context, we suggest deliberative platforms for public discussion of the consequences of a technology further blurring the boundary between nature and technology (see also Lafont, 2017; van Hove and Gillund, 2017). This could help resolve many challenges posed by genetic engineering in general and CRISPR/Cas genome editing in particular. Particularly in the context of the liability debate, follow-up research should provide a closer and more detailed investigation of

property rights issues, such as the effects of CRISPR/Cas on seed sovereignty. Further, the possibilities and challenges of open-access breeding and genetic resources require further investigation (Kloppenburg, 2014; Luby et al., 2015).

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Appendix

Glossary

Cisgenesis: transfer of genes between related (i.e., sexually compatible) varieties or species by means of biotechnological tools

DNA: deoxyribonucleic acid; molecule containing genetic information necessary for the functioning of any living organism

Gene silencing: suppression of the expression of a gene by means of biotechnological tools

Nature-identical genetically engineered organism (nGMO): organism created by a genetic engineering process that leaves no traces of genetic engineering in the resulting organism; could be the result of conventional breeding or natural evolution

PCR: polymerase chain reaction, a common method of multiplication of DNA, used among others to identify specific sequences in DNA

RNA: ribonucleic acid; multifunctional group of molecules active in coding, decoding, regulation and expression of genes

Transgenesis: transfer of genes between non-related (i.e., sexually incompatible) species by means of biotechnological tools

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