Review

Expert opinions on the regulation of plant genome editing

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Summary

Global food security is largely affected by factors such as environmental (e.g., drought, flooding), social (e.g., gender inequality), socio-economic (e.g., overpopulation, poverty) and health (e.g., diseases). In response, extensive public and private investment in agricultural research has focused on increasing yields of staple food crops and developing new traits for crop improvement. New breeding techniques pioneered by genome editing have gained substantial traction within the last decade, revolutionizing the plant breeding field. Both industry and academia have been investing and working to optimize the potentials of gene editing and to bring derived crops to market. The spectrum of cutting-edge genome editing tools along with their technical differences has led to a growing international regulatory, ethical and societal divide. This article is a summary of a multi-year survey project exploring how experts view the risks of new breeding techniques, including genome editing and their related regulatory requirements. Surveyed experts opine that emerging biotechnologies offer great promise to address social and climate challenges, yet they admit that the market growth of genome-edited crops will be limited by an ambiguous regulatory environment shaped by societal uncertainty.

Introduction

Increased availability of agricultural biotechnologies in plant breeding has forced governments around the world to accommodate, or completely overhaul, their regulatory regimes to either embrace or forgo the benefits of these technologies. The process began with genetically modified organisms (GMOs), containing foreign (transgenic) DNA, which resulted in the expansion of existing regulatory systems and the creation of new ones. In broad terms, regulatory systems assess the final products, the processes through which products are made, or a combination of both modalities. These changes have added time and cost to the commercialization of new plant varieties without obviously improving public health and safety. As innovative plant breeding technologies advance from the development of GMOs to make targeted changes in the plant’s own DNA without insertion of transgenic sequences, the question of how products of these technologies would be regulated becomes even more crucial.

Since conventional crop plant breeding (e.g., crossing, selection) is a lengthy process and getting GM varieties to market is both time-consuming and expensive, there has been pressure to develop new faster and cheaper approaches to undertake DNA sequence-specific modifications to enhance crop performance in the face of environmental shifts due to climate change (Sedeek et al., 2019). Increased knowledge of genomics has led to an evolving spectrum of techniques and technologies broadly known as new breeding techniques (NBTs). The most advanced NBTs involve genome editing that alters the plant’s genome by enabling insertion, deletion or substitutions of nucleotides via variants of site-directed nucleases (SDN) and oligo-directed mutagenesis (ODM) (Menz et al., 2020; Modrzejewski et al., 2019). The SDN technology induces the introduction of small precision modifications (SDN 1 and 2) of larger pieces of DNA or insertions of complete foreign genes at a predetermined location (SDN3). Hence, SDNs yield both transgenic and non-transgenic outcomes. ODM enables a point mutation at a predetermined location. Due to their accuracy, lower costs and application simplicity, genome editing tools can introduce valuable quantitative and qualitative traits into plants, effectively facilitating new research and incentivizing innovation.

Like any early-stage breakthrough event, the market effects of NBTs, including genome editing, are still somewhat speculative. While there are few commercialized genome-edited varieties on the market, there has been an abundance of R&D reporting in peer-reviewed articles and academic conferences, indicating that the front end of the innovation pipeline is well populated with potentially marketable products. These innovative technologies will not reach their potential unless suitable, science-based regulations are in place.

Over the last decade, there have been ongoing international discussions seeking legal clarity pertaining to the status of genome editing and derived products. Key regions around the globe have adopted different positions. In identical fashion to the regulation of GM crops, the European Union requires genome-edited organisms to undergo environmental and food and feed
risk assessments (Kawall et al., 2020). Several countries in South America (Argentina, Brazil, Chile and Colombia), as well as the United States, Australia and Japan exempt genome-edited products from regulation which, in general terms, do not contain a novel combination of genetic material and could be otherwise developed through conventionally breeding.

This article recaps key findings of a multi-year survey project in which a panel of international experts were polled about the various dimensions of genome editing that have policy implications, including their risks, their benefits, and how they should be regulated. This article is the summary of a body of work confirming that experts consider genome editing to be powerful tools for future food security that should be enabled rather than delayed.

Method
A research team at the University of Saskatchewan undertook a multi-year survey project between 2015 and 2019 involving international experts engaged in plant biotechnology to solicit their opinions about the challenges around the application of NBTs with a focus on genome editing tools.1 Given the significant role the scientific community and science-based evidence plays in informing policy choices and managing the framework for regulation, we explicitly developed the expert panel to include scientific and social experts involved in the development of new crop varieties. Surveys focused on regulatory and social barriers pertaining to NBTs (Lassoued et al., 2018b; Smyth and Lassoued, 2018), perceived benefits (Lassoued et al., 2019a), related potential risks (Lassoued et al., 2019b), costs of regulating NBT-derived crops (Lassoued et al., 2019c) and how policies should change in response to NBTs and their resulting products (Lassoued et al., 2020). A summary survey was also conducted to evaluate the overall survey project. As the survey topics varied, prospective panelists were not required to answer all surveys. Given the longitudinal nature of the survey project, the participation rate has varied as survey relevance varies among participants and over time gradually decreased, which is expected with panel studies. Thus, the sample profile slightly differs from one survey to another. For simplicity, key sample characteristics for each survey are presented in Table 1. We limited the sample profile to both regional distribution and expertise as they were the key variable in most survey analysis. Over the course of the project, our surveys were exempted from full ethics review by the Behavioural Ethics Board at the University of Saskatchewan on the basis that the participants, as experts, were not themselves the focus of the research.

Key results
Given the longitudinal nature of the study, we recognize that summarizing results of a series of surveys can be challenging. We present some of the key findings.

Use and potential benefits of genome editing
Surveyed experts ranked genome editing as the most prominent of the NBTs, with clustered regularly interspaced short palindromic repeats (CRISPR) identified as having the greatest potential to improve crop agronomic performance and to help close the food security gap by 2050 (Lassoued et al., 2018a). A large body of recent scientific proof-of-concept studies in plant breeding signal the technological promise of genome editing, and particularly CRISPR-Cas (CRISPR-associated proteins) technology, to yield a broad range of targeted and diverse traits in staples cultivars as well as in orphan crops (e.g. Brinegar et al., 2017; Dheer et al., 2020; Wolter et al., 2019). Scholars are enthusiastic about CRISPR owing to its efficiency (cost and time advantages) and accuracy at editing genomes compared to earlier resource-

| Table 1 Summary of survey topics and sample regional and background characteristics |
|-----------------------------------------------|---------------|-----------------|
| Survey topic                                | Invited       | Completed  |
| Top ranked NBTs (2 rounds of a Delphi)       | 552           | 146           |
| (Lassoued et al., 2018a)                     |               |               |
| Genome editing regulatory uncertainty        | 638           | 201           |
| (Lassoued et al., 2018b)                     |               |               |
| Genome editing social uncertainty            | 630           | 173           |
| (Lassoued et al., 2018b)                     |               |               |
| Cost of genome-edited products (Lassoued et al., 2019c) | 523 | 99            |
| Perceived benefits of genome-edited products (Lassoued et al., 2019a) | 507 | 114          |
| Perceived risks (Lassoued et al., 2019b)    | 487           | 113           |
| Regulatory reform (Lassoued et al., 2020)   | 479           | 113           |
| Summary survey                              | 450           | 83            |

1https://research-groups.usask.ca/nbt-regulation/
intensive genome editing tools such as zinger finger nucleases (ZFN) and transcription activator-like effector nucleases (TALEN) (Alok et al., 2020; Vats et al., 2019; Wada et al., 2020). CRISPR has been applied in several crops and plants including wheat, corn, soybeans, tomatoes, potatoes, oranges, banana, cassava and flowers, with rice being the most studied crop (Ahn et al., 2020; Ansari et al., 2020; Feng et al., 2013; Haque et al., 2018; Jaganathan et al., 2018; Ricroch et al., 2017). Results of the summary survey indicate that 92% of the participants assert that the application of genome editing has increased since 2015 (over the course of the project). The crops now being genome-edited are mainly cereals (61%), followed by oilseed crops (52%), vegetables (47%), fruits and nuts (34%) and pulses (27%). The accessibility and value of genome editing tools have been demonstrated in the commercialization of a few derived products in North America. The first was Calyngo oil, a high oleic soybean that produces cooking oil with less saturated fat and lower oil absorption than conventional soybean oil, sold in the US. Sulfonylurea tolerant (SU) canola, a non-transgenic herbicide-tolerant variety developed by the US-based Cibus using patented gene-editing technology, is another example of a commercially product available to American and Canadian growers.

Surveyed experts, regardless of their expertise and background, largely agree that site-specific edited crops can have greater agronomic performance (e.g. disease resistance, drought tolerance, high yields), higher product quality (e.g. nutrition, shelf life) and enhanced climate resilience, all of which would contribute to improved global food security in a faster and cheaper way (Lassoued et al., 2019a). This empirical finding lends support to several recent studies showing that genome editing has been efficiently adapted to several species of crops to improve productivity, herbicide resistance, biotic and abiotic stress tolerance and nutrition (Bailey-Serres et al., 2019; Eshed and Lippman, 2019; Hashimoto et al., 2018; Wang et al., 2016; Zaidi et al., 2019). Genome editing technology has produced a host of advantages for consumers, such as healthy oil soybeans, enhanced-flavour tomatoes, and white mushrooms (Lassoued et al., 2019a). Recent consumer research studies have shown that consumers tend to hold favourable attitudes towards gene-editing technology and derived products over GM alternatives, albeit with some variation between countries (Arias-Salazar et al., 2020; Marette et al., 2020; Mur ingai et al., 2020; Shew et al., 2018; Yang and Hobbs, 2020).

While conventional and GM approaches have shown that they can improve the yield and quality of a range of crops, the simplicity, efficiency and high specificity of genome editing make it a more economically efficient approach (Ahmar et al., 2020). Despite these benefits, experts had a diversity of opinions about the impact of genome-edited crops on trade, the environment and consumer acceptance, at least partly because relatively little is known about these aspects at this point. Only 7% of surveyed experts ranked scientific evidence as a barrier to the development and use of genome editing, but about one-quarter see political involvement as a barrier (Lassoued et al., 2018b). Our results signal that while experts trust the science they are concerned about controversies surrounding genome editing fed by non-scientific motifs. According to Qaim (2020 p. 129), ‘While the science is exciting and some clear benefits are already observable’, regulatory barriers and social perceptions of risk may impede the potential of genome editing in agriculture.

Safety considerations of genome editing

Most surveyed experts agreed that genome-edited crops—as with similar conventionally bred counterparts—pose few risks to society (76%), the economy (71%), human health (75%) and the environment (71%) (Lassoued et al., 2019b). A small minority of participants (5%) considered that these new crops pose a high risk that may require extra regulation beyond the extensive selection, testing and removal of unwanted phenotypes required before the commercial release of any new variety, regardless of the breeding method (Kaiser, 2020). The perceptions on the overall safety of genome-edited crops is consistent between scientific and social experts (P-value of Chi-square test (χ²) was less than the threshold value of 0.05), and among regions (P-value (χ²) <0.05) (Lassoued et al., 2019b). In the final project survey, experts were asked whether risks pertaining to the use of genome editing in agriculture are more or less likely to occur compared to traditional transgenic breeding. At least half of the sample agreed that allergenicity (51%), toxicity (52%), harm to non-target organisms (49%) and impact on human/animal metabolism (49%) were less likely with genome editing; approximately 40% indicated the risk are probably the same for both breeding methods. The area of highest uncertainty was weediness: only 36% of respondents thought weediness is less likely with genome-edited varieties, with another 48% asserted that both breeding methods involve the same risk.

While all breeding practices present a certain level of risk, SDN-mediated off-target changes yield a smaller number of additional genetic variants compared to those that occur spontaneously or by mutagenesis. It has been shown that computational algorithms used to design genome editing reagents, for instance, can reduce off-target changes in plants (Graham et al., 2020). Other studies showed that off-target mutations potentially induced by SDNs are of the same type as those mutations used in conventional breeding, whether occurring naturally or by physical and/or chemical mutagenesis (Lee et al., 2019; Li et al., 2019; Tang et al., 2018). These studies confirmed the number of off-target mutations produced by SDNs is lower than the number of mutations observed in conventional breeding due to spontaneous or induced mutations. Based on these findings, the European Food Safety Authority’s GMO Panel considers that the analysis of potential off-targets would be of trivial value for the risk assessment (EFSA, 2020). Thus, off-target changes in genome-edited crops do not present new or greater safety considerations compared to other breeding approaches (Graham et al., 2020).

Despite the projected safety of non-transgenic, genome-edited crops, half of the sample asserted that the biotechnology regulatory framework in their country does not favour the use of emerging biotechnologies in crop development. This was more pronounced among European participants (25% of European experts representing 30% of the surveyed panel), who indicated EU regulations completely or moderately discourage the use of genome editing, while a plurality of North American respondents (28% of North American experts representing 50% of the surveyed panel) point out that regulations only moderately discourages or has no effect on the use of genome editing (Lassoued et al., 2019b). This regional effect comparing North America and the European Union is statistically significant (P-
value ($\chi^2$)<0.05). The EU process-based system dominated by the precautionary principle has been shown to have a knock-on effect on the use of emerging technologies in many developing countries that depend on the EU market (Qaim, 2020; Zaidi et al., 2019). Despite risk assessments that conclude that GM crops are no more hazardous than conventional crops, Africa and Asia have so far largely forgone the opportunities offered by GM technology for fear of loss of access to important and longstanding markets in Europe (Zaidi et al., 2019).

Our surveys also revealed that 64% of respondents believe that advocacy groups (completely or moderately) discourage the use of genome editing in agriculture in their region, which is consistent regardless of their expertise (P-value ($\chi^2$) >0.05) or where they live (P-value ($\chi^2$) >0.05). According to Macnaghten and Habets (2020), several promising plant molecular biology innovations have been the specific target of significant social opposition and political resistance. Qaim (2020) concludes that stringent regulation and public misperceptions about risks, fuelled by consistently false narratives promoted by environmental nongovernmental organizations (NGOs), obstruct the uptake of genome editing.

### The cost of regulation

Our first survey affirmed that those in the industry believe genome editing represents a powerful breeding technology that offers significant technical and economic advantages (Lassoued et al., 2018a). With the advanced knowledge in crop genetics and the accumulated regulatory experience in plant biotechnology, these crops have the potential to deliver an increase in the number of novel traits, faster and cheaper, but only if they can get to market efficiently and quickly.

Surveyed experts estimated it could take 5 years and cost US $10.5M to develop and bring a genome-edited crop to market if regulated as a conventional crop, but up to 14 years and US $24.5M if regulated as a GM event. Some genome-edited crops can take a little as a few days to be designed at a cost of €10 (Friedrichs et al., 2019). If not regulated as a transgenic variety, these genome-edited cultivars could be markedly more cost-effective owing to the absence of further technological and regulatory testing for foreign genetic material in the plant genome. Compared to other studies (McDougall, 2011), our results show that even transgenic crops obtained via genome editing can be delivered to the market faster and cheaper than traditional GM approaches owing to the desired accuracy of genome-edited tools. In the final survey, experts were asked whether the development costs of genome-edited varieties (including regulatory compliance and preparation for introduction into the supply chain) changed over the last four years. Results showed that 34% believed that these costs are decreasing, 21% said they are about the same and 21% asserted that they are increasing, while 24% had no opinion. The cost advantage of emerging genome editing technology has been endorsed in the recent literature (Belhaj et al., 2017; Hefferon and Herring, 2017; Jouanin et al., 2018) but global efforts for coherent governance seem limited.

A few countries, including the US, Argentina and Brazil, have exempted genome-edited crops from additional regulatory oversight, provided the final variety does not contain foreign DNA. Genome-edited products free from foreign DNA and/or that do not involve plant pests risk are currently exempt from the US coordinated framework for the regulation of biotechnology. Europe is on a different track. The 2018 Court of Justice of the EU (CJEU) ruling puts the same regulatory burden on genome-edited products as have been on new transgenic crops over the last two decades (Cantley, 2012). Overall, this is judged to stifle agri-food innovation in the EU (Smyth and Lassoued, 2018).

The divergent interpretation of the risks pertaining to products of genome editing appears to be driven not by science but by political preferences, that are then formalized in legislation and regulation (Araki and Ishii, 2015; Cantley, 2012; Lassoued et al., 2018b; Wolf and Wolf, 2018). One-quarter of the surveyed experts, regardless of their location, ranked political involvement in the regulatory process as the key limiting factor in terms of innovation-related regulatory uncertainty, followed by unsynchronized approvals of new crops between countries (20%) (Lassoued et al., 2018b). Our surveys revealed that that about three-quarters of the survey sample disagreed with the 2018 CJEU ruling on directed mutagenesis, with many respondents criticizing the process-based system of EU policy governing biotechnology (Lassoued et al., 2020). Criticism of the ruling is widely shared by other scholars: Zaidi et al. (2019), for instance, assert that the CJEU decision is disappointing as it could obstruct international progress in applying genome editing technologies for crop improvement while Smyth and Lassoued (2018) anticipate a substantial impact on the future research capacity within the EU. This conflict may continue for a while as the EU environment ministries, often in conflict with agriculture and scientific research institutions, manage the rules regulating GM crops (Cantley, 2012). The EU process works to engage NGOs which has worked to transform discussions into a complex socio-political battle (Lassoued et al., 2019b).

About one-third of the panel ranked public perceptions as the most critical social barrier to the development of genome editing, linked closely to concerns about food safety (27%). This was a particular issue for the European experts we surveyed who were overall less optimistic (P-value ($\chi^2$) <0.05) about the market prospects for genome-edited products (Lassoued et al., 2018b). Europeans consumers have been found to be much less willing to accept food products derived from biotechnology of any type (Marette et al., 2020; Moses, 1999; Shew et al., 2018).

Experts also ranked trade (32%) as a key challenge to the prospects for genome-edited crops (Lassoued et al., 2020; Qaim, 2020). Smyth and Lassoued (2018) assert the CJEU ruling has further complicated the long-term competitiveness of Europeans farmers in the international market. Qaim (2020) suggests one strategy is for developing nations to ignore European attitudes and markets and seize the opportunities of gene-edited crops that would most benefit their local farmers and consumers and address their societal and climate challenges; Smyth et al. (2013) suggested industry could facilitate this by offering assistance for developing nations to realign their production and marketing systems.

### Conclusion

The gradual adoption of novel NBTs, including genome editing, are beginning to accelerate crop trait improvement. These emerging technologies offer the opportunity to improve food security and address societal challenges unresolved by conventional breeding and first-generation GMOs. We learned from biotechnology experts that the pressure from stakeholders with distinct cultural, environmental and societal concerns, divergent levels of risk tolerance and political machinations complicate governance of these novel technologies. Somewhat
encouragingly, the scientific underpinnings for expert opinions seem to be universal, which is reflected in the broadly similar results from scientific risk assessments across national regulatory systems (National Academies of Sciences and Medicine, 2016). But cross-regional analysis shows a distinct disconnect between Europe and North America, driven by inherently distinct political and cultural perspectives about benefits and risks of new technologies for food.

The division between the two key research and growing regions exacerbates the already challenging world of asynchronous use of novel biotech crops, with knock-on effects on global trade (Lassoued et al., 2020). We are already seeing a shift of R&D investment from regions with process-based regulatory systems, such as that of the EU, to countries that utilize a product-based system, which exists in most of the Americas (Lassoued et al., 2020). Surveyed experts, regardless of their background and region, accept the need to update regulatory processes to more effectively fuse a balanced range of socio-economic considerations (e.g. food security, conservation and sustainable use of biodiversity, compliance with biosafety measures) with scientific norms (Lassoued et al., 2019b). Resolving the conflict between local norms and global science could pave the way for international harmonization and the democratization of agricultural biotechnology (Eriksson et al., 2020; Macnaghten and Habets, 2020; Qaim, 2020). Qaim (2020) suggest that this will require a more honest and science-based public debate.

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Declaration of interest

None.

Author contributions

Rim Lassoued involved in conceptualization, data analysis and drafting. Stuart J. Smyth involved in conceptualization, drafting and editing, and funding acquisition. Peter W.B. Phillips involved in conceptualization, reviewing and editing, and funding acquisition. Diego Maximiiliano Macall involved in conceptualization, reviewing and editing. Hayley Hesselin involved in conceptualization, reviewing and editing.

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