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Applications, Benefits, and Challenges of Genome Edited Crops

ABSTRACT

The tools of genome editing were described more than a decade ago as promising ways to accelerate crop improvement in addition to applications for human and animal health. Now, a decade later, we are seeing applications of genome editing across a range of different crops and trait combinations that will bring benefits to producers and consumers. Countries around the world are actively engaged in updating regulatory frameworks to govern this new technology adequately. In this paper, we describe recent advances in genome editing tools, review select applications underway, consider the benefits of the technology, and offer a perspective on significant challenges to the success of the use of genome editing. Given an enabling policy environment, genome editing will be an important tool in creating a competitive bioeconomy while addressing major challenges to agriculture and consumers. We offer five recommendations to ensure genome editing in agriculture benefits society (Box 1).

INTRODUCTION

It has been just more than a decade since the tools of genome editing were fully described and functionally applied in an in vitro system that would later be recognized with the Nobel Prize (Jinek et al. 2012) and five years since the first CAST Issue Paper was published on the topic: “Genome Editing in Agriculture: Methods, Applications, and Governance.” Since those milestones, the first applications of genome editing in food and agriculture are now being commercialized (Waltz 2021, Mullin 2023), with many more in the late stages of research and development. Increasingly favorable regulatory decisions are unfolding

The application of genome editing technologies is poised to help accelerate innovation in produce and bring forward societal benefits such as improved taste, consistent availability, nutrition, increased shelf life, and reduced pesticide use. (Photo from Alpha_7D/Shutterstock.)

Box 1. Strategies to ensure genome editing in agriculture benefits society.

Five Recommendations to Ensure Genome Editing in Agriculture Benefits Society

- Increase public investments that incentivize R&D in specialty and minor use crops, identifying areas of genetic vulnerability of these crops to extend applications beyond the major commodity crops and agronomic traits that will be served by the private sector.
- Increase public investments in genomics, trait discovery, and the understanding of the genetics that inform those desirable traits to ensure applications that translate into products that serve and benefit society.
- Create incentives for start-up companies using new breeding tools to develop products that address consumer demands.
- Create incentives for developing products that have a significant positive environmental impact, especially in large acre crops that confer big scaling opportunities.
- Ensure a clearer, transparent, predictable, product-based coordinated regulatory system in the United States that does not discriminate against specialty crops and minor use applications.

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globally that should facilitate the realized benefits of the technology for the health of people and the planet.

In this paper, we build on the first CAST paper on genome editing (2018) and review advances in genome editing tool development since that paper was published. We recognize that the terms genome editing and gene editing are often used interchangeably, in addition to terms that refer to specific editing systems such as CRISPR. We will use the term genome editing in this paper.

A tremendous number of articles from around the world have been published in peer-reviewed scientific journals about methods development, specific crop applications, and trait-based breeding opportunities that researchers are pursuing using genome editing. Here, we review some of the emerging applications being developed by researchers in both the public and private sectors. We will then cover the emerging benefits of genome editing for society, emphasizing benefits for consumers, producers, and the environment (those that enhance agricultural or ecological sustainability). Finally, we uncover the persistent and emerging challenges, especially those in regulatory policy, which will need to be addressed so that the aforementioned societal benefits will be more fully realized.

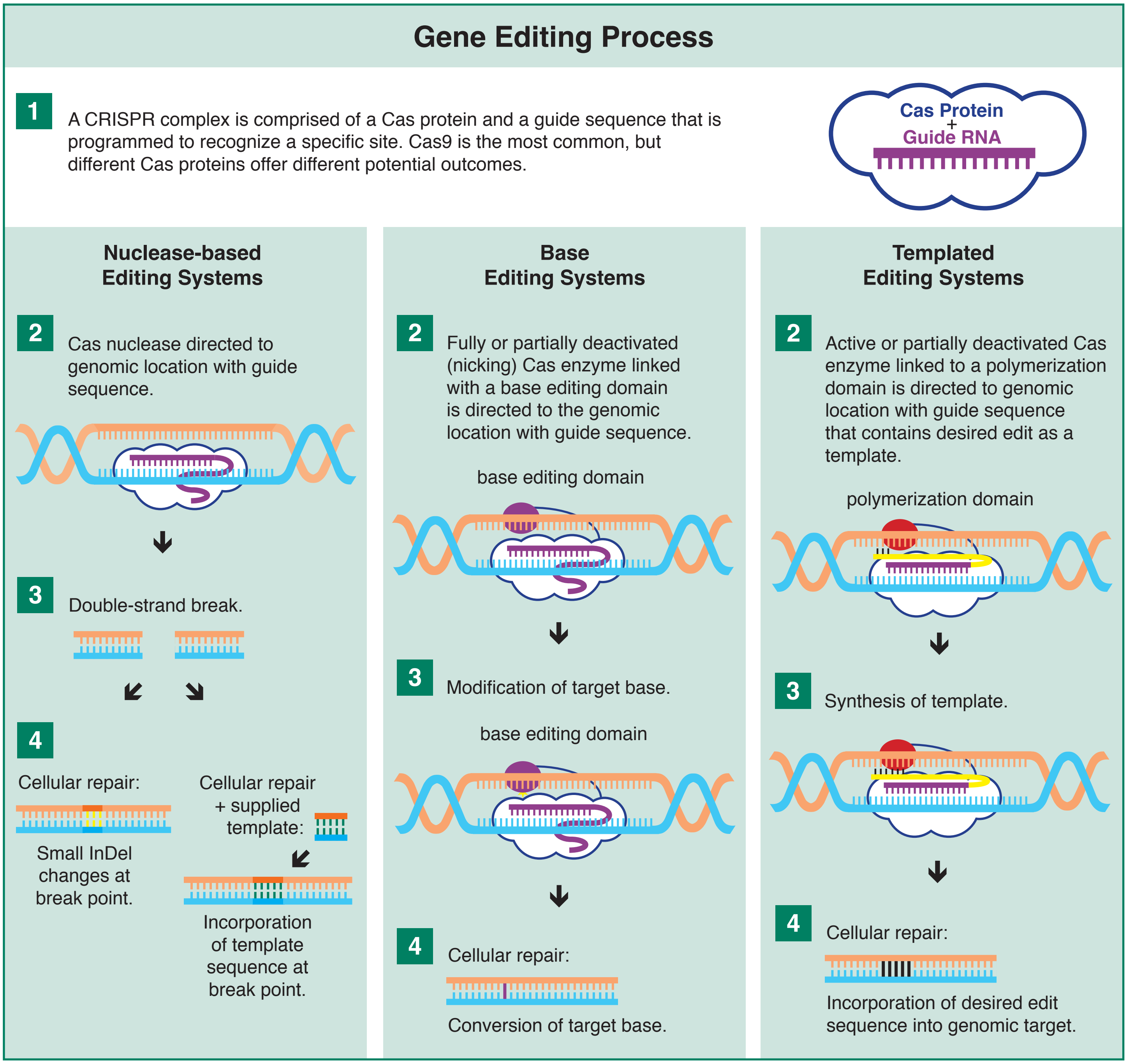
This paper focuses on applications of genome editing in crop plants that are progressing toward commercialization. In addition to reviewing the progress being made, we highlight the key challenges that need to be overcome to realize those key benefits, particularly those challenges that affect the full participation of public researchers and smaller companies, all key features of a democratized plant biotechnology enabling environment.

The theme of the series in which the last CAST paper on genome editing was published in 2018 was “The Need for Agricultural Innovation to Sustainably Feed the World by 2050.” The world continues to be challenged by many of the same issues that limit the advancements that could be accomplished through genome editing. Our ability to address major global challenges including nutrition and food insecurity in a rapidly changing climate will be determined in part by our ability to efficiently deploy agricultural innovations such as genome editing. In this paper, we call on policy makers to ensure an enabling regulatory environment for genome editing to ensure broad and impactful applications for the betterment of people and the planet.

APPLICATIONS OF GENOME EDITING

Recent advances in genome editing tools for plant applications

Genome editing is the process of modifying the genetic material of a chosen organism, generally by introducing DNA changes, such as insertions or deletions, or specific base changes in a targeted manner (Figure 1). While genome editing has been performed with many different tools and methods, such as meganucleases (Smith et al. 2006), zinc-finger nucleases (Bibikova et al. 2003), and TALENs (Bogdanove et al. 2011), the ease of genome editing with CRISPR systems has led to their quick adoption as the predominant choice in the genome editing toolbox. The name CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats) is a misnomer that generally refers to technology that is based on a bacterial defense system that has been adopted for use as a genome editing tool. In short, CRISPR systems generally rely on an enzyme, Cas9 being the most well-known, that is directed to a target site in the genome by a guide RNA molecule



Gene Editing Process

1 A CRISPR complex is comprised of a Cas protein and a guide sequence that is programmed to recognize a specific site. Cas9 is the most common, but different Cas proteins offer different potential outcomes.

Nuclease-based Editing Systems

2 Cas nuclease directed to genomic location with guide sequence.

3 Double-strand break.

4 Cellular repair:

Small InDel changes at break point.

Cellular repair + supplied template:

Incorporation of template sequence at break point.

Base Editing Systems

2 Fully or partially deactivated (nicking) Cas enzyme linked with a base editing domain is directed to the genomic location with guide sequence.

3 Modification of target base.

4 Cellular repair:

Conversion of target base.

Templated Editing Systems

2 Active or partially deactivated Cas enzyme linked to a polymerization domain is directed to genomic location with guide sequence that contains desired edit as a template.

3 Synthesis of template.

4 Cellular repair:

Incorporation of desired edit sequence into genomic target.

Figure 1. This illustration explains three of the most commonly employed genome editing approaches using a CRISPR system (although not comprehensive).

that has been designed to be complementary to the chosen DNA target. In the most basic application, the editing enzyme will subsequently bind to the target sequence and introduce a double-stranded break to the target DNA. This break triggers the cellular DNA repair process, often through the non-homologous end joining (NHEJ) pathway, which leads to small insertions or deletions (INDELs) at the break site. These INDEL mutations, if directed to the correct location within a gene sequence, can result in frame shifts within the protein-coding sequence and thus result in a non-functional protein.

It has been just more than 10 years since the first demonstration of CRISPR genome editing in eukaryotic cells utilizing the *Streptococcus pyogenes* Cas9 (SpCas9) system (Cong et al. 2013; Wang and Doudna 2023), with the first demonstration in plants to follow soon after (Nekrasov et al. 2013). While most of the first applications of CRISPR used editing enzymes as nucleases to introduce double-stranded breaks, and thus result in INDEL modifications, subsequent advances have expanded the toolkit allowing for even more sophisticated modifications including insertions of DNA cargo (Mali et al. 2013), targeted base changes (Komor et al. 2016; Gaudelli et al. 2016), and recently complete re-writing of targeted genomic locations (Anzalone et al. 2019).

Genome editing is used differently from older forms of biotechnology such as genetic transformation, which is used to create genetically modified organisms or GMOs. The primary difference is that in most applications of genome editing there is no DNA from another species ("transgenic") used to confer the desired trait. Rather, the changes that are created are genetically similar to what could have been achieved through conventional breeding or mutagenesis. However, applications could extend beyond the outcomes of conventional breeding and even facilitate the generation of highly precise insertions of foreign genes. It is easy to oversimplify the differences between the two methods, as genetic transformation can also include inserting DNA from the same species (referred to as "cisgenic") or the silencing of a plant's own gene expression.

Agronomic Traits

Private and public sectors are currently developing agronomic traits using genome editing that will benefit farmers and producers. Genome editing tools have been harnessed in several crops to obtain desired traits, including resistance to both biotic and abiotic stresses and enhancing product quality attributes by identifying and editing genes of interest. Genome editing is being applied in more than 40 crops across 25 countries, for improving agronomic traits (Menz et al. 2020).

Several groups are applying genome editing to increase yield. Examples include increasing grain quantity in wheat and kernel row number in corn (Liang et al. 2018; Nature Biotechnology 2021; O'Connor et al. 2022). Other efforts are underway to help plants adapt to abiotic stress. For example, genome editing has been used to develop rice that has increased tolerance to highly saline environments (Zhang et al., 2019. With increasing concerns about rising temperatures and limited water resources, efforts are being made to produce more thermotolerant and water-efficient crops. Examples include rice (Yin et al. 2017) and corn (Shi et al. 2017). In their review of genome editing applications for climate change adaptation Karavolias and colleagues (2021) summarize a range of specific applications underway for abiotic stress tolerance.

Applications of genome editing to protect plants from plant pests (biotic stresses) are numerous and vary in approach (Karavolias et al. 2021). Furthermore, rice, maize, and tomato have been developed with improved drought tolerance, resulting in higher yields in dry conditions (Zsögön et al. 2018; Joshi et al. 2020; Karavolias et al. 2021). Researchers are currently using genome editing to research and experimentally develop disease-resistant bananas, cassava, maize, rice, and wheat, and apple (Pixley et al. 2019). In some of these approaches, genome editing tools are applied to knock out plant genes that render them susceptible to a particular disease. For example, sugar transporters that are exploited by opportunistic pathogens (Wang et al. 2016) or hormone response genes (Shi et al. 2017).

In yet another application, Corteva Agriscience is advancing a novel approach to breeding for disease resistance in corn for Northern corn leaf blight (*Exserohilum turcicum*), Southern rust (*Puccinia polysora*), gray leaf spot (*Cercospora zeae-maydis*), and Anthracnose stalk rot (*Colletotrichum graminicola*). The concept would relocate numerous disease resistance alleles (i.e., matching genes) to a common location in the genome, which has the benefit of conferring more durable disease resistance in addition to maintaining linked traits during subsequent breeding cycles (Thatcher et al. 2023; Corteva 2023). For all plant species, this strategy of multiplexing and co-locating favorable disease-resistant genes leaves the remainder of the genome available for achieving genetic gains in other yield or quality traits by testing and leveraging genetic variation (Box 2).

Consumer Traits

With some notable exceptions, the first generation of transgenic crops were primarily large-acre row crops such as soy, corn, cotton, and canola that were improved with traits like herbicide tolerance and pest resistance. An earlier CAST publication, estimated that these traits primarily benefit producers while consumers received 20% of the overall benefits of first generation transgenic crops (CAST 2021). However, an assessment of research articles involving genome editing illustrates new opportunities to innovate in more specialty crops enjoyed directly by consumers and to deliver on traits that provide direct consumer benefits, such as enhanced nutrition, improved flavor, or longer shelf life.

Genome editing has been used to improve the nutritional quality of crops by increasing levels of vitamins and microminerals, eliminating toxicants, or introducing beneficial compounds. This can lead to healthier food for consumers and may also have economic benefits for producers when they are able to sell their crops for premium prices. For example, researchers are using genome editing to create rice varieties with higher levels of iron, which is important for combating anemia (Wirth et al. 2019); high GABA tomatoes (Nagamine and Ezura 2022) and high oleic acid soybeans; vitamin A-enhanced melons rice, banana, and tomato (Kumar et al 2022); and other crops enhanced with zinc, iron, or microminerals (Kumar et al 2022). In a study by Kaur and colleagues (2020), CRISPR/Cas9 technology was applied to increase the beta carotene content in the Cavendish banana cultivar "Grand Naine" by editing the *lycopene epsilon-cyclase* gene. The edited lines showed enhanced accumulation of beta carotene content, up to six times higher in the fruit pulp compared to unedited plants. This demonstrates the potential for using genome editing to target genes involved in regulating essential nutrients in crops like zinc, iron, amino acids, and more.

Genome-edited crops with desirable health profiles have recently become commercially available (Figure 2). The first genome edited product to be commercialized in the United States was a high oleic soybean oil, sold as Calyno (Splitter 2019), developed by the start-up Calyxt (now Cibus). In this case, the genome editing tools employed were transcription activator-like effector nucleases (TALENS). More recently, the start-up company Pairwise has built its mission around genome editing applications that will increase the appeal, convenience, and desirability of fruits and vegetables to consumers. Their product, Conscious™ Greens, was the first food product developed with CRISPR to hit the U.S. market when it entered food service in May 2023 (Mullin 2023). In this application, the company took a the mustard green, nutritious leafy green, and improved the flavor by editing out copies of the enzyme myrosinase, which is responsible for the off-putting flavors characteristic of raw mustard greens (Karlson et al. 2022). The result was a new offering in the salad category that with almost double the nutrition when compared to Romaine lettuce, bringing to market a product with a direct consumer health and convenience benefit. The start-up is also working on to remove the seeds of blackberries, which 85% of blackberry consumers say is the primary deterrent to eating the otherwise nutritious fruits. A longer-term goal of the company is to remove the pits from cherries which could be further applied to other stone fruits such as peaches and plums.

In Japan, Sanatech Seeds, a spin-off from the University of Tsukuba, used CRISPR to develop and commercialize a tomato with increased levels of Gamma-aminobutyric acid (commonly referred to as GABA) (Nagamine and Ezura 2022), a naturally occurring amino acid in tomatoes thought to have health benefits, including benefits to heart health, conferring a direct consumer benefit. Parallel efforts in Korea and the UK are developing tomatoes with increased vitamin D levels (Li et al. 2022). Other edited products are in development with direct consumer benefits, including naturally decaffeinated coffee plants (under development at Tropic Biosciences, for example) and improved natural sweeteners (by Elo Life Systems, for example).

In addition, many applications are underway that will extend the shelf life of fruits and vegetables, reducing consumer food waste in addition to other waste reductions across the supply chain (Teplitski et al. 2023). Those include non-browning mushrooms (Waltz 2016), non-browning avocados (Green Venus 2023), and non-browning lettuce (Green Venus 2023). Okanagan Specialty Fruits was a front runner in 2017 with their commercial release of bioengineered through

Box 2. Agronomic Traits Case Study: Banana.

Agronomic Traits Case Study: Banana

The application of CRISPR/Cas9-based genome editing in banana was first successfully demonstrated using the visual marker gene *phytoene desaturase* (*PDS*) (Kaur et al. 2018; Naim et al. 2018; Ntui et al. 2020). This breakthrough in CRISPR/Cas9-based genome editing for bananas opens up possibilities for developing improved varieties with enhanced agronomic traits.

At the International Institute of Tropical Agriculture (IITA), researchers are working on developing a banana resistant to diseases, such as banana Xanthomonas Wilt (BXW) disease and banana streak virus. BXW disease is devastating the banana production in East Africa, impacting the livelihood of millions of smallholder farmers. The knockout of the *Downy mildew resistance 6* (*DMR6*) gene in the BXW-susceptible banana cultivar ‘Sukali Ndiizi’ has been shown to enhance resistance to BXW disease (Tripathi et al. 2021). The banana mutants targeting the *MusaDMR*6 orthologue were generated using CRISPR/Cas9. The *dmr6* edited events exhibited enhanced resistance to BXW without any observed morphological abnormalities. Further, disrupting the *MusaENODL3* gene in the BXW-susceptible cultivar ‘Gonja Manjaya’ demonstrated enhanced resistance to BXW disease (Ntui et al. 2023).

Another application of CRISPR/Cas9 technology in bananas involves inactivating the endogenous banana streak virus (eBSV) integrated into the genome of plantain. BSV is a virus belonging to badnaviruses, which integrates into the host plant genome, creating significant challenges in banana breeding and germplasm movement. Tripathi and colleagues (2019) successfully edited all three open reading frames (ORF) of the viral genome using CRISPR/Cas9, resulting in targeted mutations in the integrated eBSV sequences. The genome-edited plants of ‘Gonja Manjaya’ showed targeted mutations in the integrated eBSV sequences in the host genome. Most of the genome edited plants remained asymptomatic compared to the control non-edited plants under water stress conditions, confirming the silencing of the reactivation of eBSV into infectious viral episomal proteins.

Many cultivated banana varieties have tall growth habits and are prone to lodging and damage during storms. To address this issue, researchers have been striving to develop semi-dwarf and dwarf banana varieties. Shao and colleagues (2020) demonstrated that CRISPR/Cas9 technology could be used to develop semi-dwarf plants by editing the *Musa acuminata gibberellin 20ox2* (*MaGA-20ox2*) gene, thereby disrupting the gibberellin (GA) pathway in the banana cultivar ‘Gros Michel’. By targeting the GA gene, which plays a crucial role in determining plant height, researchers were able to achieve a desirable semi-dwarf phenotype.

Banana is a climacteric fruit that ripens quickly and starts decaying within a week. This fast-ripening process poses storage, transportation, and marketing challenges leading to postharvest waste. However, through CRISPR/Cas9-mediated genome editing researchers have successfully targeted the *aminocyclopropnae-1-carboxylase oxidase* (*MaACO1*) gene in bananas, resulting in delayed ripening and extended shelf life of the fruit, as shown by Hu and colleagues (2021). The edited banana fruits exhibited reduced ethylene synthesis, the hormone responsible for ripening, thereby enhancing their shelf life under natural ripening conditions. Additionally, Tropic Biosciences has developed non-browning gene-edited bananas. These non-browning bananas have been reviewed and determined to be non-genetically modified organisms (non-GMO) in the Philippines and are now in field trials (Tropic 2023).

Examples of successful product development through genome editing.

Calyno High Oleic
Soybean Oil
by Calyxt
(TALENS)

Sicilian Rouge
High Gaba Tomato
from Sanatech Seeds
(CRISPR)

Conscious
Greens
from Pairwise
(CRISPR)

Waxy
Corn
by Corteva
(CRISPR)

Figure 2. Four products that as of the date of this publication have been successfully developed for commercial use using tools of genome editing (either TALENS or CRISPR). These products are not all currently on the market but did achieve regulatory approvals for commercialization.

RNAi non-browning Arctic® apples. The company is now employing the tools of genome editing to develop new products displaying consumer and agronomic traits in apple, cherry, and other fruits (Carter, personal communication).

Other public researchers and genome editing start-ups are addressing traits that will help introduce new healthy fruit and vegetable options into the market that currently are not widely grown, marketed, or consumed. These include highly nutritious goldenberries, ground cherries (Lemmon et al. 2018), and black raspberries (under development by Pairwise), none of which have been previously subject to sufficient breeding efforts to render them commercially viable. Genome editing offers new opportunities to introduce novel fruits and vegetables with health benefits, providing new healthy options to consumers.

Product Quality

Many end-use quality characteristics, such as the flavor or texture of cooked, baked, distilled, or brewed food and beverage products are controlled by many genes, making plant breeding time-consuming and inefficient. Genome editing can be used to study genes that participate in starch, protein, oil, polyphenol, and antioxidant pathways to validate their function and expression and assist in targeted breeding. Further, genome editing can be incorporated into the plant breeding process by directly modifying multiple genes involved in a pathway. Nevertheless, end-use quality characteristics with relatively simple genetic underpinnings remain the fastest and easiest to develop using genome editing.

One example is the high-amylopectin or “waxy” grain phenotype in cereals. Waxy grain can be created by turning off the genes that produce amylose starch (Gao et al. 2020). In the absence of amylose synthesis, the grain contains 95–100% amylopectin starch, which is the type of starch that gives sticky rice its unique, slightly sweet texture. Amylopectin has a lower melting point than amylose, making it more digestible in animal and yeast systems, including in craft malting and brewing applications. Amylopectin also imparts a moister crumb to baked goods like breads, cakes, and cookies.

Benefits: Social, Economic, Environmental

Examining benefits to society (farmers and consumers), the economy, and the environment need to be firmly situated within the sustainable development and intensification frameworks. In practical terms, viewing climate change or ecological/environmental considerations in isolation without considering the economic and social aspects can lead to development outcomes that are not sustainable and/or are outright rejections of innovations. Despite the examples above, very few crops derived using genome editing approaches have been commercialized or reached markets. Those that have reached markets include soybeans and tomatoes (Menz et al. 2020) and, more recently, salad greens from the mustard family (Mullin 2023). Other crop varieties are under development but not close to market release. Waxy corn, described in the previous section and developed by Corteva Agriscience was developed and successfully reviewed by the USDA.

However, in the end, the product was not commercialized in the United States because of the lack of regulatory clarity in countries that would be importing grain and/or by-products from the United States.

Realized and documented impacts through social, economic, and environmental assessments have been identified in several robust reviews for other crop improvement approaches including conventional plant breeding and genetic transformation (National Academies of Science 2016; De Steur et al. 2017) Defining sustainable development or sustainable intensification has been controversial and often confused with other related terms including climate-smart agriculture, eco-efficiency, and crop intensification terms (Kuyper and Struik 2014; Tittonell 2014). This may be because of ambiguously defined terms that may even be contradictory (Struik et al. 2014). This paper will use the Royal Society (2009) definition of sustainable intensification as those forms of production where crop yields can be increased without adverse environmental impact and the cultivation of more land.

Examining benefits derived from the use of genome edited approaches and products will eventually need to be expanded to consider the three pillars of sustainable development and intensification. Here, we explore the three pillars: social, environmental, economical, and will point out where other pillars may be impacted, although the documented and purported “main” impact is highlighted in each category.

Genome editing benefits society

Genome editing is a powerful tool that has the potential to revolutionize agriculture by enabling precise and targeted crop modifications. As discussed in the previous section, genome editing applications can help increase crop yields limited by biotic and abiotic stressors including disease resistance, improved nutrient uptake, and tolerance to adverse growing conditions. The technology can also be used to increase the nutritional quality of crops by modifying genes that control the synthesis of vitamins, minerals, and other essential nutrients. For example, researchers have used genome editing technology to experimentally develop rice varieties that contain higher levels of iron and zinc, which can help to address micronutrient deficiencies in developing countries (Wirth et al. 2019, Nagamine and Ezura 2022).

Benefits to the economy

Genome editing can be used to improve crop yields, increasing production while keeping other inputs and resources constant, thereby contributing to food security. By modifying specific growth and development genes in plants, researchers can enhance crop productivity. For instance, researchers have used a genome editing technology to experimentally develop a wheat variety that produces up to 30% more grain than current commercial varieties (Liang et al. 2018). In corn, genome editing resulted in a 20% increase in the number of kernel rows (Nature Biotechnology 2021; O’Connor et al. 2022).

A 2023 report by the Breakthrough Institute and the Alliance for Science examined the economic risk of “saying no” to genome editing by not adopting enabling policies. The authors conclude that the forgone benefits of not adopting genome editing applications (what they refer to as new genomic technologies or NGTs) in food and agriculture range from 171 to 335 billion Euros annually.

Environmental benefits

Another important aspect of genome editing’s potential societal benefits is environmental. Genome editing can play a potential role in reducing the negative effects of climate change on agricultural production, as well as reducing the negative effects of agricultural production on greenhouse gas emissions (GHG). Crop improvements have long been important in U.S. agriculture for adapting to increasingly extreme weather. Moscona and Sastry (2023) find that agricultural innovation directed towards adaptation (primarily, conventional breeding of more adapted crop varieties) has offset about a fifth of the economic impacts of U.S. agriculture from damaging weather trends since 1960. Lee and colleagues (2022) forecast changes to U.S. corn yields in response to projected climate change for the remainder of this century under different scenarios and compare these to the estimated yield gains from traits introduced into corn by genetic transformation since the 1990s. From this comparison, they find that the predicted yield shortfalls from future climate change are roughly three to six times the previously observed gains from first-generation transgenic corn varieties. These analyses speak to the importance of crop improvement and the magnitude of the challenge to maintain agricultural production in the face of climate change. Game-changing agricultural innovations like genome editing are key to meeting this challenge.

Genome editing can be used to develop crops that are resistant to pests and diseases, thus reducing the need for pesticides and other agricultural chemicals. This can have positive effects on the environment and human health, in addition to offering cost savings to farmers. For example, researchers have used genome editing to experimentally develop tomato plants that are resistant to the devastating tomato yellow leaf curl virus (TYLCV) and reduce the need for chemical pesticides (Chandrasekaran et al. 2016). Genome editing has also been used to experimentally develop crops that have pest and disease resistance in bananas, maize, rice, tomato, apple, and others, in some cases with a focus on food-insecure areas in Africa where there may be limitations to conventional crop protection tools (Tripathi et al. 2022; Jiang et al. 2018; Abdallah et al. 2015; Carter, personal communication).

Genome editing can help reduce agriculture’s environmental impact by developing crops and varieties that are more productive while requiring fewer resources or in resource-limited environments, leading to sustainable intensification. For example, researchers have used genome editing to experimentally develop drought-tolerant maize and other crop varieties that require less water than current varieties (Joshi et al. 2020; Shimizu et al. 2018). By increasing production and productivity, genome edited varieties may help reduce the land required to produce food and other biomass needed to feed people and animals (WRI 2019).

In addition, as explored by Teplitski and colleagues (2021), applications of biotechnologies, including genome editing, can help reduce food loss and food waste, which accounts for 8%–10% of global greenhouse gas emissions and costs the global economy more than $1 trillion each year (WRI 2023). If current trends persist, food loss and waste is predicted to double by 2050 (WRI 2023). Technologies like genome editing are poised to help address this challenge with work at Okanagan Specialty Fruits and Green Venus offering early examples.

Karavolias and colleagues (2021) review the potential applications of genome editing for agricultural adaptation to climate change and highlight a range of promising advances in improving productivity and nutritional quality, as well as increasing resilience to extreme weather and disease pressures. Less research has been done on using genome editing for climate mitigation (e.g., carbon sequestration) in crop farming, but here there is also promise. Jansson and colleagues (2021) advocate for modern biotechnologies being applied to develop crops for "carbon farming" by designing plants (e.g., via genome editing) with increased root strength and enhanced photosynthesis, in conjunction with fostering complementary soil microbial communities. From a public policy perspective, it is also worth pointing out recent large increases in U.S. government funding for "climate-smart agriculture" (USDA 2023), including foundational and applied R&D on improving carbon sequestration and climate resilience in crops (USDA NIFA 2022). These climate priorities are also articulated in a recent Executive Order from the U.S. government on advancing the bioeconomy, including the goal to "develop genetic engineering and technology tools for high yield crops and forest trees with deeper and more recalcitrant root systems to increase soil organic carbon" (OSTP 2023).

Other Benefits

Genome editing generates genetic variation

In addition to the three pillars of sustainable development and intensification discussed above, genome editing also offers other intrinsic benefits to plant breeders as well as maintaining and encouraging crop diversity. Genetic variation is critical for plant breeders focused on crop improvement. Genetic variation refers to the diversity in plant genomes that results from natural or induced mutations and is then acted on by natural or artificial selection. Diversity within a plant species provides breeders with the opportunity to harness genetic variation by introducing new traits into elite varieties of interest.

Preserving and broadening the genetic diversity within a crop species is important because it creates a reservoir of desirable traits that can be called upon for long-term breeding and adaptation work. However, breeding for a new variety necessarily involves narrowing its genetic variation over time as improvement cycles retain only the best-performing offspring and discard the majority of offspring that do not perform well enough to be a competitive commercial product. Plant breeders must continually search for approaches that increase genetic variation within their species of interest to continually improve the performance of consecutive varieties. Genome editing offers an opportunity to increase such genetic variation at specific desirable loci in the genome while leaving the remaining favorable genes unchanged. Genome editing can be used to unlock usable genetic variation by creating or restoring desirable chromosomal arrangements that have selection value to breeders (Schwartz et al. 2020).

Genome editing may also facilitate the generation of novel variations that would not be generated by natural processes like recombination (Schleif et al. 2021). For example, new alleles of plant promoters produced by genome editing have resulted in the development of myriad traits like larger tomato fruit and altered rice grain starch quality (Rodríguez-Leal et al. 2017; Zeng et al. 2020). By targeting multiple guides to the promoter of genes, new types of genetic diversity that correspond to significant variation in important traits have been produced. This genetic variation not typically present in the gene pool can provide the basis for meaningful crop improvement and can be especially important in cases where there is insufficient genetic or phenotypic variation for a specific desired trait in the gene pool.

Genome editing preserves food qualities in unadapted germplasm

End-use quality traits impacting things like flavor or baking quality in food crops historically have been very difficult to select for, so the breeding process can be long and expensive, especially in species with a long lifespan. Most end-use quality traits are sequestered in unadapted germplasm (like landraces) that is difficult to work with in commercial settings due to having specific requirements for local adaptation, such as light or thermal sensitivity or photoperiod effects of latitude. When these materials are crossed with elite materials with the goal of creating novel commercial varieties or hybrids, the progeny fail to thrive outside of their source environments. In some cases, cross-incompatibility mechanisms hinder intermating them with elite commercial materials. For these reasons, adapting plants carrying end-use quality traits from one geography to another is very challenging. This explains why, for example, there are delicious and varied masas (nixtamalized dough used for making tortillas, tamales, etc.) throughout Mexico, but they are almost nonexistent in commercial breeding programs in the United States despite a large, interested Hispanic/Latino community and the excellent infrastructure for growing maize.

Given the pace of climate change, plant breeders and local communities need to work together to save unadapted germplasm with food-quality traits that have significant cultural value by disentangling interactions between ecological adaptation, reproductive biology, and end-use quality. The same set of genes that have historically enhanced local adaptation are now becoming maladaptive in the same location.

Genetic mapping populations can be developed for the specific purpose of clarifying the functional genomics of quality traits, identifying causal genes and favorable alleles, and packaging them within more heat- and drought-tolerant genetic backgrounds to ensure that foods having significant cultural value will be around for many years to come. Indeed, mapping population designs, statistical and genomic resources, and advanced algorithms can identify candidate genes and favorable alleles underpinning desirable traits more efficiently than ever before. However, once they are identified, methods are needed to rapidly induce genetic variation in elite germplasm that lacks those traits. Transformation methods are becoming more effective on a wider range of genotypes within a number of species, so once we identify genes impacting desired quality traits, genome editing can be used to rapidly validate gene functions for precision breeding or to remove barriers to ecological adaptation by modifying physiological pathways (e.g., photoperiod sensitivity or reproductive incompatibility) that would make quality traits difficult to express in new or rapidly changing environments.

Overall, the use of genome editing in agriculture has the potential to benefit society, the economy, and the environment by facilitating crop improvement, increasing crop productivity, reducing the use of pesticides and herbicides, improving nutritional quality, and reducing the environmental impact of agriculture. However, despite enthusiasm for the technology, promising scientific advances, and early hopes for its democratized and broad use, challenges to commercialization remain. Researchers are making progress in addressing certain technical bottlenecks, such as developing plant transformation and tissue culture protocols, as well as growing the understanding of the connection between the genotype and phenotype to obtain desirable traits for broader ranges of plant species. In the section that follows, we focus on market and regulatory challenges that will be key determinants of how impactful the tools of genome editing will ultimately be.

Challenges

Market Acceptance

It remains to be seen how the marketplace and consumers will respond to genome edited food products, as the first few such products are just starting to enter markets. Consumer attitudes towards food are determined by a complex array of socioeconomic and cultural factors. Affordability, subjective tastes, nutritional value, and some safety aspects are obvious factors in purchasing decisions. However, other attributes, such as environmental or health impact, which cannot be directly observed but rely on consumer trust in product claims and labels can also heavily influence consumer choice. There is significant heterogeneity in perceptions along with (and which is likely to correlate with) variation in consumer values and preferences for these attributes (Costanigro and Onozaka 2020). This heterogeneity significantly limits what we can currently predict *ex ante* about future consumer attitudes toward specific genome edited foods that are poised to enter supermarkets and restaurants.

With these limitations in mind, it is still instructive to draw lessons from recently published studies examining consumer willingness to pay (WTP) and broader perceptions regarding genome edited food, all of which so far have been based on hypothetical choices and attitudes that consumers report in surveys or lab-based studies rather than from direct experience and observed purchases. One consistent finding across these studies is that consumers' average stated WTP for genome edited food is lower than for food produced through conventional methods, but higher than their WTP for transgenically produced (i.e., genetic modification [GM]) food, holding constant other attributes of the product (Shew et al. 2018, Muringai et al. 2020, Yang and Hobbs 2020, McFadden et al. 2021, Hu et al. 2022, Ortega et al. 2022).

Beyond this consistent result, current studies have produced ambiguous findings about how the type of information and communication mode affects consumer WTP, and how different types of consumers are likely to respond to genome edited products in the market. Yang and Hobbs (2020) conducted a consumer-stated choice experiment with a sample of 804 Canadian adults to examine WTP for apples genome edited for consumer-oriented health- and appearance-related benefits (e.g., enhanced antioxidants, non-browning). They find that using a narrative in explaining the technology versus a "logical, scientific" presentation of facts increased WTP for genome edited apples. Similarly, from a survey-based choice experiment regarding orange juice purchases with 1,096 U.S. consumers, Hu and colleagues (2022) found that using infographics and video to explain the technology led to higher WTP for genome edited orange juice. However, McFadden and colleagues (2021) conducted another study of 1,185 U.S. consumers to gauge the receptiveness of genome editing technology to combat citrus greening disease in Florida orange juice production. In contrast to Yang and Hobbs and Hu and colleagues, they find that providing a video-based narrative about the impact on farmers of citrus greening appeared to reduce consumer WTP for genome edited orange juice.

Regardless of how large or small the average WTP for genome edited foods may be, there is likely to be wide variation in the choices of individual consumers, and understanding these differences is likely to be more useful for anticipating future changes in attitude. In a lab-based study of U.S. and French consumers stated WTP for non-browning genome edited apples, Marette and colleagues (2021) conclude that their finding of lower average WTP for genome edited food is driven down primarily by a minority of consumers (43% in France and 19% in the United States) who state they would boycott genome edited products.

These cross-country differences were also found by Shew and colleagues (2018) in an early WTP study of genome edited rice (in their case, a production-oriented weed control trait) across five countries (Australia, Belgium, Canada, France, and the United States). Marette and colleagues also find that the average benefits to consumers of the non-browning characteristic outweighed the negative value towards the genome editing attribute in the U.S. sample but not in the French sample, and that additional information provided to consumers about the technology reduced aversion in the French sample but not in the U.S. sample.

Differences in labeling laws across countries are also important to consider in the context of these WTP studies. Genome edited foods in the United States may not require labeling, in contrast to the "Bioengineered" label that GM foods are legally obligated to carry. In the European Union genome edited foods currently fall under the same regulations as GM foods, which require labeling any food that contains greater than 0.9% GM ingredients. EU regulations regarding genome edit plants are currently being revised and will be addressed through EU Parliament vote(s). In other jurisdictions, such as Brazil and Japan where GMO labeling is required, once a genome edited product is reviewed and found to be not a GMO, it is treated as conventional and not subject to GM specific labeling. Such variations between countries will almost certainly affect consumer behavior and perceptions towards genome edited foods.

Synthesizing the conclusions from the WTP studies described above, it is clear that information content, communication mode, consumer trust in the sources of this information, and highly heterogeneous consumer values within and between countries will shape consumer attitudes towards these products. At this point in time, the consistently higher reported WTP for genome edited versus GM food suggests an opening for developers of these products to engage in more dialogue with consumers and the public to build mutual understanding and trust, a conclusion which is mirrored in the broader literature on public perceptions of genome editing. Strobbe and colleagues (2023) provide an overview of consumer and stakeholder perceptions literature on genome edited foods. Synthesizing this literature, they find a widespread lack of familiarity with the technology among the public across studied (high-income) countries. They also identify widespread skepticism about whether consumers and farmers will actually benefit the most from the technology compared to other food system actors, as well as concern about who will effectively oversee the governance and regulation of technology. They also conclude that there is growing support in the United States and other countries for labeling genome edited food.

A study published by the Alliance for Science (2022) that focused on U.S. consumer perceptions of genome editing in agriculture reinforced the notion that few people are informed about genome editing. Only one-quarter of respondents say that they are very or somewhat knowledgeable about genome editing. However, sentiment about genome editing improves with additional information. Notably, focusing on explaining the difference between genome editing and GMOs does not improve sentiment. However, explaining the possible benefits and applications does increase positive sentiment. The specific benefits of genome editing in agriculture seen as the most beneficial are (1) improving yield to address food security in regions affected by climate change, (2) reducing chemical inputs that affect clean water supplies, (3) reducing the price of food (4) developing crops resistant to disease, drought, and insects; and (5) reduce the amount of water used in farming. In a five-year study from 2018 through 2022 in which favorability and sentiment toward biotechnologies as presented in social and traditional media, Lynas and colleagues (2023) conclude that the favorability and sentiment of genome editing in media is more positive than other biotechnologies. The authors note that the conclusions are based on arbitrary timeframes chosen for the study.

Ultimately, public perceptions of genome editing in agriculture will be strongly conditioned on how and what actual products are deployed within food systems. Henderson and colleagues (2023) conducted the most comprehensive, systematic review to date on the broad socio-cultural factors related to the acceptability of genome editing in agriculture (crops and animals). This survey highlights a number of key themes that help contextualize the above discussion within the existing food system: First, widespread mistrust of large companies developing agricultural biotechnologies, among large groups of the public across countries, means that *who* deploys the first applications is likely to be as an important a factor in public perception as *what* or *whom* the application actually is benefitting. Additionally, prior societal experience with GM crops suggests that traits that primarily benefit farm production rather than consumer-oriented quality aspects are likely to be met with more public ambivalence, particularly given the majority of the public’s lack of direct experience with farming. Another important aspect that Henderson and colleagues raise is the consistent finding that public perceptions are generally more favorable towards genome editing in crops versus livestock. In all these aspects, the current landscape for genome edited crops appears favorable.

The first whole food genome edited product developed with CRISPR to enter the U.S. market, Conscious™ Greens, is a product improved for consumer traits (a highly nutritious product improved for flavor) and was developed by a start-up company, Pairwise. The product was first launched into food service in May of 2023. As the company looks forward to bringing future Conscious foods products to market, they committed to including a voluntary icon that indicates the technology and the benefit ("Better flavor through CRISPR" for example) (Evanega et al. 2024). Thus, the first CRISPR-developed product to enter the U.S. market, and the second genome edited product, addresses these primary concerns of consumers and should, therefore, help to set a positive path forward for genome edited crops in the United States and beyond (Box 3).

To maintain this favorable public landscape, developers should seek to be inclusive and responsive to stakeholders with diverse values and to be as transparent as possible about the nature of genome editing applications, the distribution of benefits, their safety, and their potential risks. Transparency was another key theme raised by Henderson and colleagues as a public concern, with desired labeling being a key factor in consumer surveys. Finally, we largely lack any evidence on the perceptions and WTP for genome edited food among the public and consumers in low-income countries, and Henderson and colleagues point to this as a significant research gap. Since these countries are where the majority of the population and economic growth is expected to occur for the rest of this century, it is critical to better understand attitudes toward for different genome edited foods in these contexts.

As mentioned, public acceptance will likely be impacted by the entity responsible for developing the genome edited food. Current commercialization efforts have been limited to groups in the private sector. Greater participation of academic, non-governmental, and governmental organizations in the development of commercial genome-edited projects may contribute to greater public favor of the technology overall. Products developed by these organizations may also offer unique benefits to the consumer, environment, and society overall that could garner additional public favor. Addressing barriers to participation for developers beyond the private sector is paramount to market acceptance and the success of the technology.

Box 3. Case Study: Conscious Greens Consumer Activation Events.

Case Study: Conscious Greens Consumer Activation Events

In May 2023, the agriculture and food tech start-up Pairwise launched into food service the first genome edited product developed with CRISPR to hit the U.S. market, Conscious™ Greens. In the run up to the launch, three consumer activation events were held in or near the cities of Seattle, Washington; Palo Alto, California; and Austin, Texas at festivals that attract a wide range of different consumers. Across the three events, 6,050 Asian-inspired and blackberry summer salads were served to attendees of the festivals, free of charge. Descriptions of the technology used to develop the greens were shared in a few different ways: (1) on the back wall of the booth, (2) via QR codes on table tents, and (3) verbally by brand ambassadors. Three thousand one hundred twelve surveys were completed by consumers who ate the salads. Ninety-one percent of consumers indicated that they were "very likely" (61%) or "somewhat likely" (30%) to purchase the genome edited salad greens. Although there was no survey question specifically on the reception of the technology, there were two open ended questions that offered consumers the opportunity to comment on the technology if the technology was front of mind. Those questions were, "What if anything did you like about the salad (please be specific)?" and "What, if anything, did you not like about the salad (please be specific)?" In response to these questions, fewer than 0.99% of respondents made any negative reference to the genome editing technology used to develop the greens and 0.7% offered positive comments about the technology. These results are the first data that assess consumer reaction to a tangible genome edited product that survey respondents were able to consume prior to completing the survey.

Governance

The lack of global synchrony in the approach and timing of the review of genome edited crops has tempered enthusiasm for and slowed the commercialization of crops developed using the tools of genome editing (Schmidt et al. 2020). In the United States, the regulatory uncertainty and various regulatory approaches from the multiple federal regulatory agencies highlight the challenges of not only global but also domestic lack of regulatory alignment (Jenkins et al. 2021).

The U.S. regulatory system for products of biotechnology involves three federal agencies, the United States Department of Agriculture (USDA), the Food and Drug Administration (FDA), and the Environmental Protection Agency (EPA) under the Coordinated Framework for the Regulation of Biotechnology (CF) federal policy. First published in 1986 and updated in 1992 and 2017, the CF specifies the applicability of each agency's existing laws to provide oversight for biotechnology products based on their intended use. In the case of crops, the underpinning statutory authorities are the Plant Protection Act for the USDA for the intended use of planting, importation, and movement, the Federal Insecticide, Fungicide, and Rodenticide Act for the EPA for the intended use as pesticides, and the Federal Food, Drug, and Cosmetic Act for EPA and FDA for the intended use as human and animal food. While no new biotechnology laws were passed, each of the three agencies established regulations and guidance specific to biotechnology products.

In light of emerging plant breeding tools such as genome editing, as well as in consideration of the decades of regulatory experiences, the USDA and EPA published revisions to their biotechnology regulations. The USDA established two overarching categories of exemption. Acknowledging that "plants created through conventional breeding have a history of safe use related to plant pest risk" and that "the types of plants that qualify for these exemptions can also be created through conventional breeding", the USDA established the following exemptions:

- The genetic modification is a change resulting from the cellular repair of a targeted DNA break in the absence of an externally provided repair template; or
- The genetic modification is a targeted single base pair substitution; or
- The genetic modification introduces a gene known to occur in the plant's own gene pool or makes changes in a targeted sequence to correspond to a known allele of such a gene or a known structural variation present in the gene pool.

Appreciating that these exemptions are a sliver of what could be done through conventional breeding or occur in nature, the USDA built into the regulation the ability "to exempt plants with additional modifications, based on what could be achieved through conventional breeding." USDA recently published a proposal for five additional exemptions for modified plants (Docket No. APHIS-2023-0022), providing a public comment period until January 19th, 2024, at which time there were 6,477 public comments on the docket.

Further, the USDA's 2020 final rule replaced event-by-event regulatory approval with regulatory review based on plant-trait-mode of action (PTMoa). The USDA published the specific combination of PTMoa that has been reviewed and determined by the USDA to be not regulated. The list of PTMoa determined to be unregulated by USDA continues to grow as the Agency completes its review of the new PTMoa.

For plants that qualify for exemption, the USDA does not require notification. However, the USDA did establish voluntary exemption confirmation mechanisms for developers who wish to consult with the USDA. For plants that do not meet the current exemptions, the USDA established the Regulatory Status Review (RSR) for the agency to determine the regulatory status.

Since the publication of the final rule in 2020, many developers have sought confirmation of exemption from the USDA (Figure 3); several have sought an RSR for new PTMoa's, and all are published on the USDA website[1].

EPA's regulatory oversight is limited to a subset of plants. Specifically, the EPA's regulatory scope is the plant-incorporated protectant (PIP) expressed in plants. Following the advent of Bt-crops, EPA codified regulation for PIPs in 2002. At the time, EPA recognized that plants naturally produce PIPs, therefore, the EPA exempted PIPs that are introduced into a plant using conventional breeding from premarket review and registration under FIFRA, as well as tolerance requirement under FFDCA. With genome editing applications, EPA recognizes that they can be used to create PIPs that are similar to those that could have been done through conventional breeding or occur in nature. In July 2023, EPA published a final rule establishing two new exemption categories:

- PIPs created through genetic engineering from a sexually compatible plant that meet specific criteria. This category can be divided into two subcategories, (1) where the PIP is created through an insertion of a native gene and (2) the modification of a native gene. To constrain the expression level of the created PIP, the insertion of the native gene must produce a pesticidal substance identical in sequence to the pesticidal substance identified in the source plant, and any regulatory regions inserted as part of the native gene must be identical in nucleic acid sequence to those regulatory regions of the native gene identified in the source plant. In the case of subcategory 2, the modification of an existing native gene must match corresponding polymorphic sequence(s) in a native allele of that gene from a single source plant.
- Loss-of-function (LOF) PIPs where the genetic material of a native gene is modified to result in a direct pesticidal effect through the reduction or elimination of the activity of that gene.

The EPA requires all LOF PIPs to be notified to the Agency prior to use. Applicants are not required to but may seek EPA's confirmation of LOF exemption status. Developers of PIPs created through genetic engineering from a sexually compatible plant are required to undertake a mandatory premarket process to confirm "eligibility" for the exemption. Both new categories of exempted PIPs are subject to a recordkeeping requirement not imposed on conventionally bred PIPs. Further, any PIPs created through genetic engineering from a sexually compatible plant that do not qualify for the exemptions would be subject to full EPA registration requirements.

Like the "conventional breeding" exemptions in the USDA's regulation, the EPA exemptions are extremely narrow compared to the breadth of plant modifications and PIPs that *could* be created using conventional breeding or occur in nature. Unlike the USDA regulation, the EPA's rule did not include any mechanism to add new exemption categories.

As of this writing, the FDA has not taken further action since requesting public comment on genome editing in new plant varieties used for food in 2017. While we await the FDA's long anticipated clarification of its policy for the regulation of products derived from genome editing techniques, we can reflect on the FDA 1992 policy statement on new plant varieties and its applicability to new plant varieties developed using genome editing. The 1992 policy statement recognized that plant breeding methods represent a continuum, from a traditional crossing of two varieties to using molecular methods to introducing genes from other species into a targeted plant species. Genome editing would be considered part of this continuum, with different applications of genome editing fitting into the continuum of plant breeding methods.

In considering the different products of genome editing applications in plants, genetic changes can range from small or large number of nucleotide changes, nucleotide deletions or additions, to recreating an allele from a wild relative in a commercial variety, to chromosomal rearrangements, to moving native genes or clustering them in a specific region of the genome, to introducing a transgene in a site-specific manner. Several of these genome editing applications could be observed in nature, as well as be accomplished, albeit more slowly and with less precision, through more traditional plant breeding methods, such as crossing a commercial variety with a wild relative or inducing mutations. This is an important point to factor when considering the potential for any novel food safety risks. Other products of genome editing applications, such as introducing a gene from an unrelated species, are similar to genetically engineered products that currently go through the FDA voluntary, formal consultation process.

Therefore, the 1992 policy and the following statement remain relevant:

> *The regulatory status of a food, irrespective of the method by which it is developed, is dependent upon objective characteristics of the food and the intended use of the food (or its components). The method by which food is produced or developed may in some cases help to understand the safety or nutritional characteristics of the finished food. However, the key factors in reviewing safety concerns should be the characteristics of the food product, rather than the fact that the new methods are used.*

Successful plant breeding and cultivar improvement requires leveraging many science and technology-based disciplines including, but not limited to the following: genetics and genomics, bioinformatics, agronomy, molecular biology, chemistry, plant physiology, plant pathology, entomology, data science, statistics, digital imaging, engineering, and biotechnology. Improving crop cultivars across all plant species is a unique blend of all the above, and not the least of which is biotechnology.

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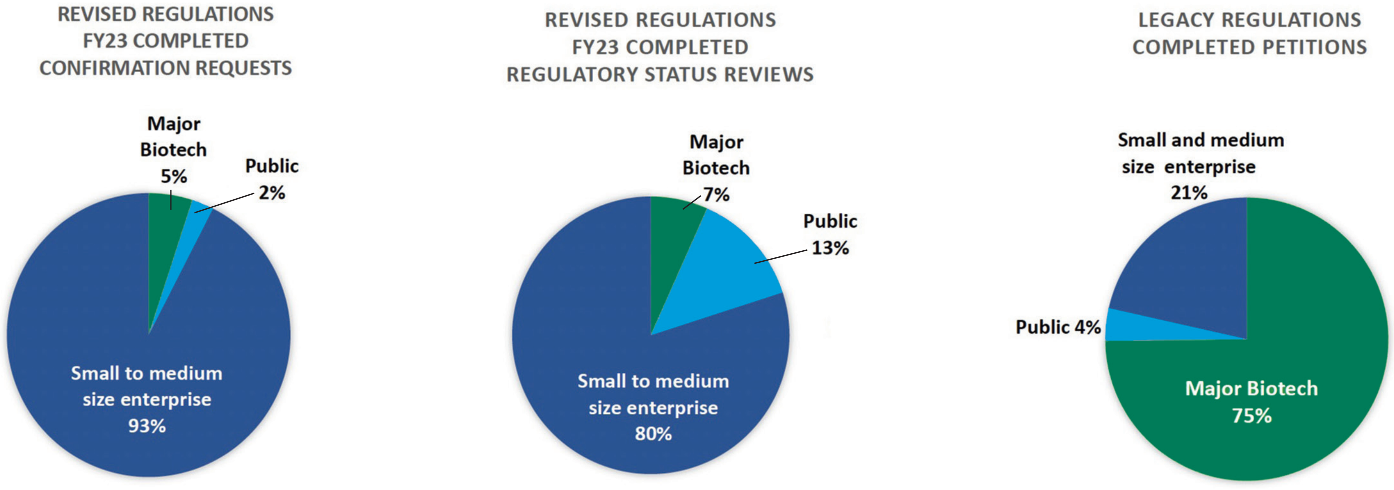
[1] https://www.aphis.usda.gov/aphis/ourfocus/biotechnology/regulatory-processes/rsr-table/rsr-table

Among these sciences and technologies, products developed with genetic transformation have received the greatest degree of regulatory oversight. Over more than three decades, multiple U.S. federal administrations have attempted to position regulatory oversight of our U.S. policy agencies in a coordinated framework towards a science and risk-based approach. Despite these well-meaning attempts by multiple United States federal administrations, the regulatory hurdles globally and in the United States have remained complex and lengthy, enabling only the largest companies in the private sector to invest research dollars for the long and costly journey of product development and regulatory approval, and only in major large field crop species. In the past, this situation has left out the vast majority of the diverse plant species that comprise substantial portions of our food systems, as well as public sector and small to medium-sized private sector breeding programs. Given the current status of genome editing and regulatory limitations, there is a risk of going down a similar path as GMOs, where only the largest multinational companies can afford to invest in the technology in a limited number of crops. The public sector and a large number of private sector organizations, from large multinationals to start-up companies, are now well positioned in the United States to be global leaders in improving and fully using genome editing; however, the investments in development will be stymied in the near future if U.S. policy agencies don't act soon to clarify and simplify their regulatory approaches.

With new products and technologies being developed, regulations are highly fluid and contentious. One of the oft debated proposals is by Gould and colleagues (2022). They propose omics-based molecular techniques for assessing whether new crop varieties, regardless of methods of development, should be subject to additional safety testing rather than the current framework. However, this proposal is contrary to the regulatory revisions that are currently occurring domestically and internationally. This means that significant work would be needed to move towards such a system in the United States and possibly other countries.

The Coordinated Framework emphasized that regulatory evaluations should be based on product outcomes, not on the process or technology used, such as genome editing. In the short term, regulatory agencies should consider the following when implementing regulatory exemption criteria: (1) The plant species has a safe history of food, feed, fuel, and fiber use; (2) All genes involved within the genome editing target are cisgenic (i.e. contained within the gene pool of that species); (3) Genome structure of the species, whether it is a diploid or a polyploid should be considered irrelevant to the applicability of the exemptions; (4) The types of traits (agronomic based,

Requests moving through the U.S. regulatory process reflect an increased diversity in technology developers.



Small to medium size enterprise is defined as a business with no more than 250 employees and $1B in annual revenue.

Figure 3. Compared to under the legacy deregulatory petition process, without any exemptions from regulation (chart on right), we see an increase in applications from public research entities and small to medium enterprises with new processes at the USDA that aim to facilitate regulatory review. Plants that meet the criteria for exemption from regulation may go through the Confirmation Request Process to confirm they are exempt from regulation. Plants that do not fit the exemption criteria for stated exemptions can go through the Regulatory Status Review Process. Based on data presented at the United States Department of Agriculture (USDA) Biotechnology Regulatory Services Annual Stakeholder Meeting, Nov. 15, 2023, https://www.aphis.usda.gov/brs/pdf/2023-stakeholder-meeting.pdf.

disease resistance, favorable nutrition, environmental sustainability, etc.) should not further increase the regulatory hurdle; and (5) The number of genes being edited should not increase regulatory action, provided (1) and (2) above apply.

Genome editing enables more efficient combinations of desirable traits into improved varieties; the favorable variation for a specific trait could exceed the short-term genetic variation of what has been documented through conventional plant breeding technologies. Even as long ago as 1992, the Office of Science and Technology Policy issued an update to the Coordinated Framework on biotechnology that set expectations of a risk-based, scientifically sound basis for the oversight of activities that introduce biotechnology products into the environment (57 FR 6753), thus affirming that U.S. federal oversight should focus on the traits of the product, the environment into which it is being introduced, and the intended use of the product, rather than the process by which the product is created. Advances in biotechnology, commercial product outcomes, and the history of the plant breeding process to develop new safe varieties demonstrate that a sound science and risk-proportionate approach are sufficient to ensure safety.

Conclusion & Recommendations

The magnitude of the global challenges before us calls for new technologies that will help us positively improve and sustain our food system while improving the health of the planet. Genome editing is one tool that will play an important role. Emerging data suggest that the public is prepared to embrace technology that will improve the health of both people and the planet. The challenge before us now is to create the enabling environment that will allow the tools to have their promised impact. A facilitative enabling environment will spur research and development using the tools of genome editing, incentivize innovation, realize an efficient and science-based regulatory system, and offer transparency and proactive engagement with consumers and other stakeholders. We put forward the following policy recommendations that, if enacted, would help us realize the potential of genome editing for social good:

- Increase public investments that incentivize R&D in specialty and minor use crops, identifying areas of genetic vulnerability of these crops to extend applications beyond the major commodity crops and agronomic traits that will be served by the private sector (Bate et al. 2021).
- Increase public investments in genomics, trait discovery, and the understanding of the genetics that inform those desirable traits to ensure applications that translate into products that serve and benefit society.
- Create incentives for start-up companies using new breeding tools to develop products that address consumer demands.
- Create incentives for developing products that have a significant positive environmental impact, especially in large acre crops that confer big scaling opportunities.
- Ensure a clearer, transparent, predictable, product-based coordinated regulatory system in the United States that does not discriminate against specialty crops and minor use applications.

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