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REVIEW

Gene Editing: The Next Breakthrough Technology in Our 10,000-Year Journey of Crop Improvement

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Abstract

Humans have improved plants for their utility through selective self-pollination, crossing, and progeny selection for >10,000 years, largely based on physical characteristics. Less than 200 years ago, the genetic basis of heritability in selection was revealed, enabling breeders to accelerate genetic gain. Breakthroughs in genomics and molecular markers for the past century have enabled breeders to locate and select genomic regions affecting desirable traits, improving breeding precision. Transgenesis has enabled crop insertion of desirable exogenous genes, enabling *de novo* functionality. These technologies, along with agronomic practices, have generated more than sixfold yield improvements in crops such as corn in the past century. Gene editing, with its unique ability to precisely edit, change expression, and move genes *within* a crop's genome, has the potential to be the next breakthrough technology. For this to come to fruition, it is critical to take a holistic view considering perspectives of scientists, farmers, regulators, and consumers.

Introduction

Genes have shaped the reproduction, adaptability, and survivability of all life on earth, including the plants we depend on for food, through their ability to continuously iterate and evolve. For most of history, the genetics behind these variations and iterative changes were unknown. Rather, selection relied exclusively on what could physically be seen, tasted, and measured (Fig. 1).

Today, many plant varieties are so modified from their wild-type progenitors that they are unable to survive in the wild. In many cases, the cultivated varieties are so different from existing wild relatives that it is hard to identify their ancestry. From an evolutionary perspective, these dramatic changes were accomplished by early plant breeders in a very short time, for the past 10,000 years.

In the mid-1800s, Gregor Mendel studied the heredity of physical traits such as flower color, height, and pubescence using pea plants, providing the necessary framework for heredity-based plant breeding.[1] As the laws of genetic inheritance were further advanced in the early 20th century, they were quickly applied toward the improvement of plants. Scientists and breeders recognized that there was a vast amount of genetic variability in plants and that the scientific community had only begun to tap its potential.[2]

A central figure in The Green Revolution of the 1950s and 1960s was the plant-breeding scientist Norman Borlaug, who with colleagues crossed thousands of wheat lines from around the world and ultimately developed a high-yielding disease-resistant variety.[3] Those early varieties frequently lodged, or fell to the ground, because they were so heavy with grain. Borlaug and team developed new wheat varieties that were shorter and more resilient to disease. These varieties, along with new dwarf strains of rice and other cereals in Asia and India, helped stave off massive starvation, earning Borlaug the Nobel Peace Prize in 1970.[4]

Since Borlaug's first applications of Mendel's early experiments, the fundamentals of plant breeding have remained largely intact. Scientists and breeders strive to select plants that produce the most desired characteristics. With the discovery of DNA as the hereditary material in the 1940s, scientists have gained extraordinary insights into plant genetics, which has led to great advances in food security.

The first plant genome (*Arabidopsis thaliana*) was sequenced in 2000, and today we have genome sequences for numerous crop plants.[5] As a result of deeper understanding of underlying genetics, farmers today produce more crops on less land than their predecessors a century ago. In 1920, according to the U.S. Census, the farm acreage in the nation totaled nearly 936

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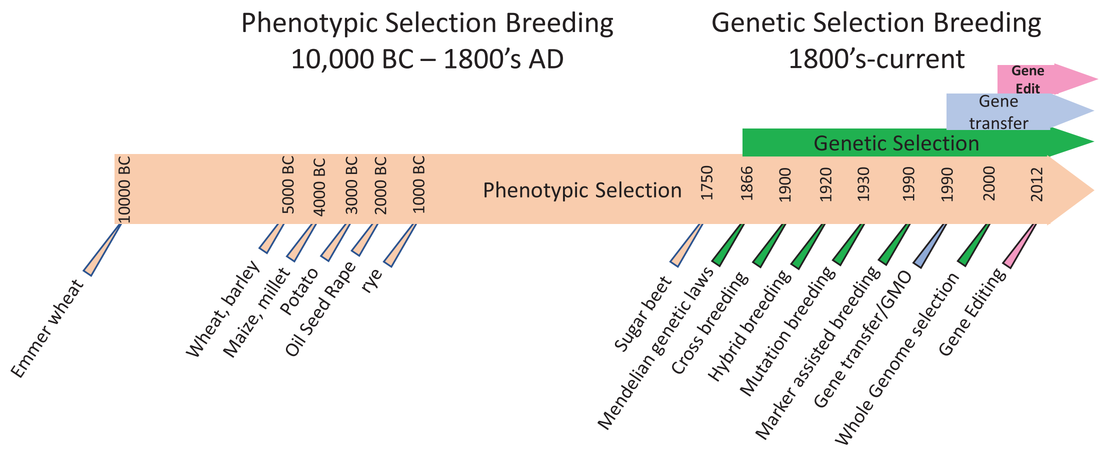

FIG. 1. Historic timeline of crop domestication and genetic technologies used for crop improvement.

million acres. In 2020, the total U.S. acreage dedicated to agriculture stood at 896 million acres.[6] During the same time, population grew from 106 million to 329 million in 2020.[7] All of this occurred while reducing the workforce involved in agriculture from 30% of the population in 1920 to <1% now.[8]

As the world population grows to an estimated 9.7 billion people by 2050, we will need to double food production and reduce waste to feed the planet. Today, some 820 million people are considered undernourished, due to many factors, including transport, accessibility, as well as production, according to the World Health Organization.[9] Climate change and its impacts on soil and water quality as well as pest and disease distribution will also need to be managed carefully to improve food security around the world. For the past 50 years, human impact on climate has resulted in an estimated 21% drop in agricultural productivity.[10] This is equivalent to losing 7 years of production. Plant breeding will need to accelerate the rate of improvement for the next 30 years to prevail amid climate change and population growth; deploying new technology to enable this will be obligatory.

Biotechnology Transformed Crop Production

The ability of genetic improvement techniques such as breeding and genetically modified organisms (GMOs) to provide innovations necessary to maintain stable food supplies cannot be underestimated.

GMOs, transgenics, and biotech traits are all synonymous in the field to infer the insertion of a gene encoding a trait of interest from one species into another. The gene as well as its regulatory elements (promoters, terminators, expression modulators, presence markers, etc.) are designed and engineered into a genetic "construct." This construct is then integrated into the genome of the plant of interest, or transformed, using particle bombardment,[11] agrobacterium-mediated transformation,[12] or electroporation.[13] For the past 40 years, the technology used for improving the efficacy, precision, and efficiency of discovering and developing biotech traits of interest has greatly improved.

Elite germplasm can now be directly transformed with transgenes, whereas in the past only "tissue culture friendly" lines could be used.[14] Expression of genes can now be targeted to certain tissues where efficacy is needed (e.g., roots for corn rootworm efficacy) and away from other tissues (e.g., pollen) to ensure pollinator safety.[15] The ability to precisely guide transgenes to desired locations in the genome has also been developed, allowing pyramiding and breeding efficiency.[16]

In 1990, an enzyme used in cheese production and a yeast used for baking became the first food products developed from biotechnology.[17] Six years later, a soybean variety resistant to glyphosate herbicide, became the first biotech trait designed for benefiting agricultural production, and transforming weed control in row crop agriculture.[18] Since then, farmers have been growing crops shaped by biotechnology innovations.

Transgenic Bt corn creates its own insecticide, made possible by a gene from *Bacillus thuringiensis* bacterium.[19] Insect-resistant transgenic crops have played a significant role in lessening the amount of chemical pesticide inputs. Between 1996 and 2018, the use of pesticides by farmers dropped by nearly 9%, largely due to the adoption of genetically modified (GM) crops that were more resistant to pests and herbicides.[20]

Early generations of herbicide-resistant crops such as glyphosate and glufosinate-resistant crops[21] transformed corn and soybean production in the Americas, greatly simplifying and improving weed control. Although these herbicide-resistant genes are still present in most GM crops, newer systems such as the Enlist herbicide resistance system[22] enable a larger number of weed species to be controlled.

As of 2019, 14 biotech crops have been planted in in 29 countries, including the United States, which commands nearly 40% of all land dedicated to biotech crop production globally. Today, the majority of corn, cotton, and soybeans planted in the United States are GMO varieties.[23] Among these 29 countries, 24 developing countries contributed 56% of the total global biotech acres.

In Africa, seven countries (South Africa, Sudan, Nigeria, Ethiopia, Malawi, Kenya, and Swaziland) have approved planting of biotech crops in 2020, an increase from three countries in 2018. Approximately 3 million hectares of maize, soybean, and cotton containing GMO traits were planted in these six countries in 2019. In late 2019, Kenya approved the cultivation of Bt cotton with the first farmer cultivation in 2020, reducing the need for insecticide treatments. Mozambique, Niger, Ghana, Rwanda, and Zambia are also making significant progress in the establishment of regulation frameworks, research, and acceptance of biotech crops.[24]

In Latin America, Brazil is the largest producer of the 10 nations in the region that produce biotech crops, with a focus on soybeans, maize, cotton, and sugarcane. India, the fifth-largest producer of biotech crops, had >6 million farmers planting Bt crops in 2019. Today, nearly 2 billion people worldwide now have access to food produced from biotech crops.[24]

In the 1980s, a coordinated framework was developed in the United States between U.S. Food and Drug Administration (FDA), the U.S. Department of Agriculture (USDA), and the Environmental Protection Agency (EPA) to regulate biotech plants. In 1994, the first GM food—a tomato—was available for purchase to American consumers, followed by several other crops, including Bt corn and a variety of herbicide-tolerant crops.[25] By the turn of the 21st century, more than half of soybean and crop acreage in the United States was dedicated to GMO production.

In addition to herbicide or pesticide tolerance, GM crops can provide a number of agronomic improvements, including better yield and drought resistance profiles, lower nitrogen use, and a greater resilience to viruses.[26] In corn, for instance, the increased expression of the zmm28 protein leads to higher yields.[27] The papaya ringspot virus is another example. It was first detected in Hawaii 80 years ago and began impacting papaya crop yields in 1950s.[28] A GM papaya was introduced in 1998 that proved to be effective in resisting the virus. It became known as the Rainbow papaya and by 2010, it accounted for >90% of Hawaii's papaya production.

Prohibiting GMOs can, in many cases, impact the quality and availability of certain foods.[29] Despite lingering public distrust of GMO foods, the American Association for the Advancement of Science recently concluded that GMO foods are no riskier than consuming food produced from conventional plant breeding.[30]

GMOs can increase nutrition, increase land productivity per hectare, lower pesticide use through in-plant protection, reduce soil compaction, and enable no-till production systems. Their intrinsic ability to deliver protection to the plant through the seed, rather than external applications, offers growers significant benefits in ease of use and stability, while helping protect crops defend themselves from pests or disease, enabling higher yields and productivity.

Navigating the Global GMOs Regulatory Landscape

The massive shift in R&D investment from ag chemistry to biotechnology for the past 30 years has also ushered in a complex and challenging regulatory environment around the world. When ag biotechnology was first developed, there was no regulatory framework. That changed quickly, as governments sought to ensure no unintended consequences would emerge and to assure the public that the technology is safe as it is released into the environment.

The prevailing thought from the agriculture industry at the time was that regulatory burdens would be eased as it developed a track record of success for safety and security. However, the opposite occurred. Disparate regulatory policies, processes, requirements, and timelines proliferated across the globe. Each country and region has its own set of regulations with virtually no alignment. Countries such as the United States and Brazil are among those with established predictable policies, whereas approval requirements and timelines of GMOs for import in China and Mexico are often less predictable. Policies can be politicized, often not based on science, and impede innovations reaching the market quickly and effectively, despite an impeccable record of GMO safety.

For instance, when developing a new biotechnology trait corn product, a developer must gain approval from multiple regulatory agencies around the world before it can bring the product to growers' fields, as the grain produced will often be traded on the global market. The costs associated with such complex regulations are onerous. For each new seed biotech trait developed between 2008 and 2012, it took an average of 13 years and $136 million in costs to bring that product to market, including $36 million in regulatory costs.[31]

The "Quiet" Work of Genomics Applied to Plant Breeding

Genomics' impact on crop productivity, yield, adaptation, drought and disease resistance, nutrition, and novel varieties has been significant. For the past 30 years, much of the attention in agricultural genetics has been around biotechnology traits. However, in the background, building the genetic foundation upon which to deliver highly efficacious biotech traits, tremendous strides have been made in both understanding qualitative and quantitative native genes within the crop genome, and applying that knowledge to crop improvement.[32]

Genetic markers were first used to map the linkages of genes in *Drosophila*.[33] Since then, linkage analysis techniques have continued to advance and be applied to every major agricultural crop, as well as many other plants, to impute their relative location and linear arrangement on chromosomes. In the 1980s and 1990s, molecular markers were used to identify and "tag" genes that produced desired traits. In addition, they were used to precisely select progeny containing multiple desired genes from a breeding population, thus pyramiding multiple useful disease genes into one parent.[34] The use of Random Amplification of Polymorphic DNA[35] and Amplified Fragment Length Polymorphism[36] have become important molecular marker tools for linkage to desirable genes that improve agronomic performance.

Eventually, single nucleotide polymorphisms emerged as a tool to provide very high densities of genetic markers, capable of detecting subtle differences in alleles. Subsequently, high-throughput genetics laboratories, aided by end-point PCR technology, have emerged as a standard tool for breeding institutions, giving breeders deep visibility into the genome of the crops they develop.[37]

As molecular marker technology became more ubiquitous and affordable, breeders began saturating crop genomes with markers, developing associations that link genetic information to phenotypic or field performance. In doing so, they develop "training sets" of relevant germplasm tested in many replications of their target environment, to create associations between genomic markers field performance (yield, plant height, and disease tolerance), and potentially any trait that can be measured.

These training sets can then be extrapolated against the whole genome profile of novel breeding crosses to impute or predict the field performance.[38] As progeny can be evaluated without expensive field characterization, this fundamentally changes the selection scheme breeders use. This process rapidly improves the genetic gain per breeding cycle because only progeny predicted to have favorable performance are included (or kept) in the breeding cycle, essentially "stacking the deck" with the predicted winners.[39] Breeders can then choose whether to use this acceleration of genetic gain to "substitute" for early cycles of progeny testing (release new varieties sooner), or to achieve a greater level of genetic gain from each breeding cycle (release better varieties with normal timelines).

As field performance data collection improves and accelerates with the use of real-time sensors, drone and satellite imaging, streaming real-time environmental and weather data and plant growth parameters, these data sets can also be built into algorithms and associated with genomic data to give further resolution and predictive power of selection, while increasing genetic gain per breeding cycle.

Likewise, as genome sequencing costs continue to decrease, breeders can saturate the genome with even more markers, or to eventually sequence the genomes of each progeny, associate this deep genomic information to increasing multiparameter performance and phenotypic information to further accelerate improvement. Whole-genome sequence data can also help breeders identify "dormant" or "highly preserved" regions of the genome and start unlocking structural variation, which could also be associated with performance and used for selection.[40]

The use of genomic and molecular information within modern breeding programs does not in any way "modify or change" the genome, it just exposes its composition. Breeders still need to "find" the most desirable progeny in their large breeding populations, but the technology enables them to do so quickly and more precisely than any previous breeding technology. Because the genome is not changed, the use of these technologies within breeding programs is not subject to regulatory approval. Using whole-genome predictive breeding enables accelerated genetic gain per cycle, and the release of new elite varieties and hybrids, each better than the previous generation, at a much faster pace. The technology is applicable to all breeding programs, and can rapidly accelerate progress in crops that have long growing cycles (perennials, trees, etc.)[41]

Robust genomic information tied to real-world field trial data can rapidly improve gain per breeding cycle. However, with increasingly unstable weather patterns and ecological disruptions, the need for more predictive breeding algorithms and future-casting programs is growing.[42]

Genomics continues to be an immensely powerful tool at our disposal. New innovations are necessary, however, to deal with challenges associated with a growing population and climate change. The continued evolution of genomic approaches will greatly expand the ability to meet future food security challenges.

Enter—Gene Editing

Although breeding has been the foundational technology for plant improvement for thousands of years, it is relatively slow, and each cross or generation essentially "re-shuffles the deck," necessitating a large investment to sort through and "identify" the winners within that population—those containing the gene or genes of interest. Biotechnology leaves the genome essentially unperturbed (except for the small insertion of the transgene); however, this technology has limitations on both the numbers of genes that can be improved, as well as a complex and nonharmonized global deregulation process that adds time and cost to any innovation.[43]

With the advent of gene-editing technology, scientists and plant breeders can now make precise changes to individual genes, or throughout the genome, whereas leaving the remainder of the genome unperturbed, preserving the genetic gain investment used to generate elite varieties. Gene-editing tools such as CRISPR, TALENs, zinc fingers, and meganucleases can search a genome for a specific DNA sequence and make precise edits to that site.

The CRISPR method of gene editing (marked by the 2020 Nobel Prize in Chemistry) uses a programmable guide RNA to direct a Cas9 nuclease to cut a particular DNA sequence. At the cutting site, specific repairs can be made by adding or deleting base pairs (or entire genes) to delete or disrupt the gene, improve the functionality of the gene, or add new functionality.[44]

The most effective use of gene editing comes from its ability to edit genes already located in the target plant's genome. Single genes can be targeted to impact their functionality or arrangement on the chromosome.[45] Although gene editing may resemble transgenesis, as the first steps are performed in a tissue culture laboratory, it is fundamentally different than transgenesis in how it is used. The technology involves temporarily moving the tools (CRISPR-Cas9, guide RNA, and DNA repair template) into the plant cell through tissue culture. As the edited cells regenerate into plants, progenies are genotyped to validate the desired edits, and are then tested in greenhouses or field environments to validate the desired effect. Finally, the selected variant edited locus can be developed directly as a product, or used for further breeding, introgression into other germplasm, or pyramided with other desirable loci (Fig. 2).

Gene editing can be used to colocate desirable genes around one genetic locus to enable breeding efficiency in either forward-breeding or backcrossing.[46] Breeders need only select for one locus, rather than many throughout the genome, improving their efficiency and gain from selection. In addition, colocating desirable genes in familiar "desirable" locations of the genome, can detach them from less-desirable genes, which otherwise would be carried in each breeding generation (Fig. 3).

Newer gene-editing technologies, such as base editing or prime editing, give the ability to make point mutations—base

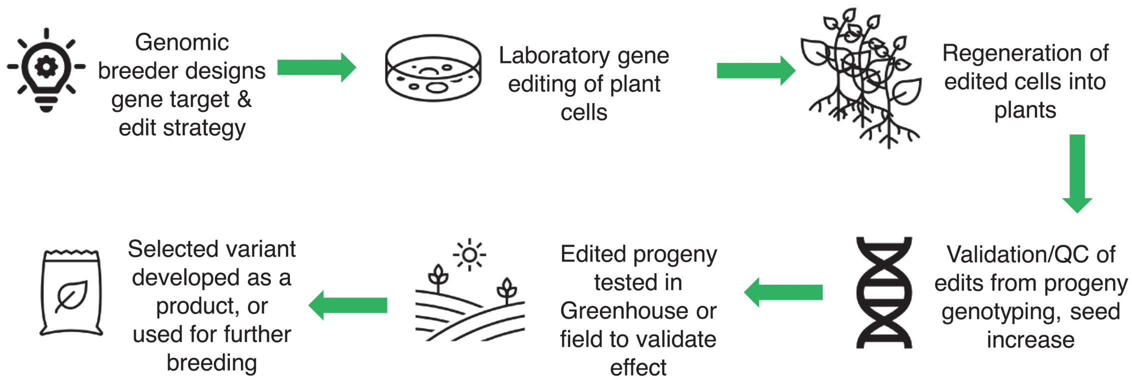

FIG. 2. General process steps for gene editing for crop genetic improvement.

pair changes, small insertions, or deletions, in the DNA strand without creating double-stranded breaks and homology directed repair. Base editing and prime editing offer advantages in efficiency, fewer by-products, and lower off-target edits.[47] Finally, gene editing can also be multiplexed with multiple editing targets within one experiment, to edit genes involved in entire pathways, turn on or off predicted desirable or undesirable genes, or create new variation in parts of the genome with low variation or frequency of recombination.[48]

Because of the robust functionality, diversity of applications, and ease of use, gene editing fills a niche that neither genomic-assisted breeding nor transgenesis has enabled. The technology has the potential to transform breeding from a process that primarily "identifies" the desirable genotype to one that through multiple edits of various forms (deletions, insertions, colocations, and bulk-editing) can "create" the desirable genotype. Gene-editing technology is a step change in our ability to improve plants, and as such will be a critical tool in meeting the demands of global food security.[49] Academics are investigating the potential of gene editing for pathway engineering[50] and for creating variation that can be used within breeding programs to further improve genetic gain. Products derived from simple edits using gene-editing technology are starting to emerge on the market from start-up companies. Some of these products include high-oleic soybeans and Sanatech's GABA tomatoes.[51]

Gene Editing in Support of Global Challenges

Gene editing comes with several potential benefits that could greatly help feed and protect our changing planet, starting with healthier foods. Gene editing can help reduce the number of allergens found in food along with the levels of saturated and trans fats. In addition, it can enhance the nutritional value of popular crops and foods such as peanuts and wheat. One example is high oleic soybean oil, derived from gene editing.[52] This heart-healthy oil, developed commercially by Calyxt, has zero

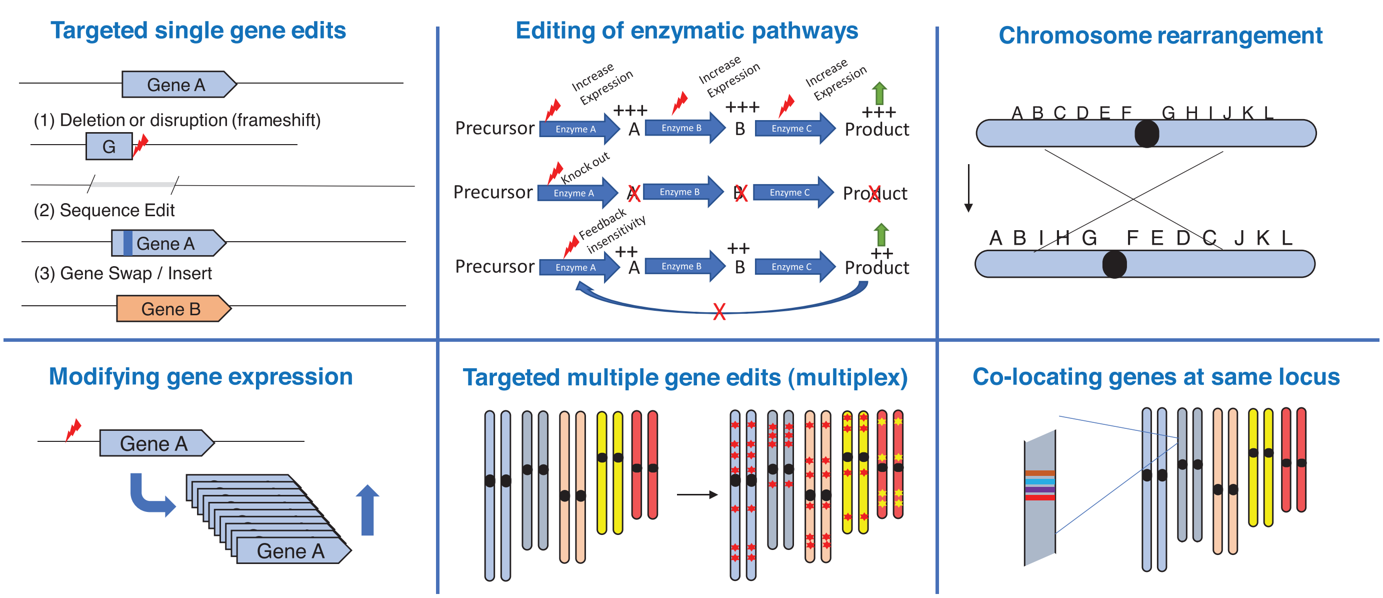

FIG. 3. Potential functionalities and applications of gene editing for crop genetic improvement.

trans fats, longer shelf life and performs well in baking and frying. Researchers used gene editing to create a soybean variety that was higher in monounsaturated fats and compete effectively with oils such as sunflower, canola, or olive oil.[53]

Researchers at the Innovative Genomics Institute are using gene editing to improve cassava, a dietary staple for nearly one billion people worldwide. Without sufficient processing, the plant can cause cyanide poisoning in humans, which can lead to neurological disorders. In three different cassava varieties, new gene editing advances have completely prevented cyanogenesis.[54]

Another important advantage of gene editing is its implications for better crop health and environmental health. Every year, it is estimated that we lose 15–20% of the soybean crop to diseases. In the global droughts of 2012, for instance, about 9% of soybean yield was lost. Disease and environmental stress such as drought are important factors that prevent the soybean (and most other crops) from reaching their full yield potential.[55] Gene editing is also helping crops resist more rapidly evolving and spreading diseases, as well as adapt to new environmental realities that are emerging with a changing climate (Fig. 4). There is an urgent need for new climate-resilient crop varieties, and this tool has the potential to help us breed them more quickly and more precisely than conventional breeding.

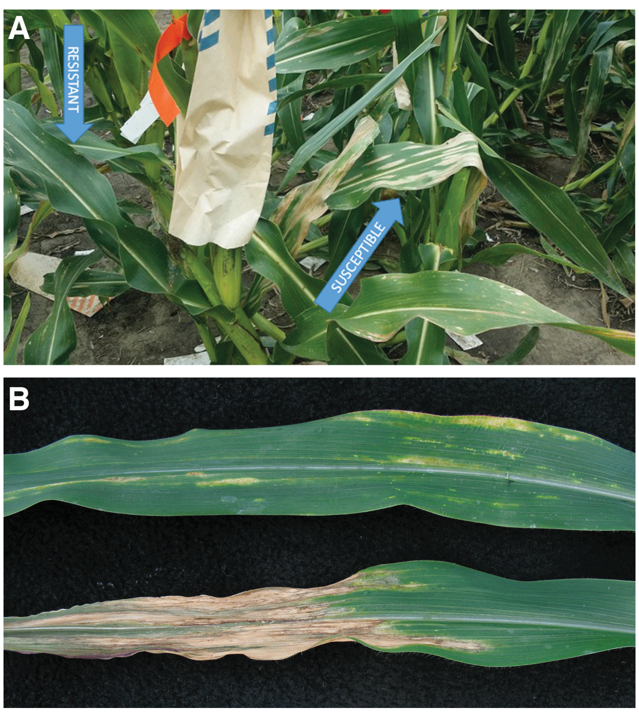

FIG. 4. Gene editing technology improves tolerance to maize foliar diseases.

(A) Leaves of resistant (edited) inbred and susceptible (non-edited) inbred plants in the field.

(B) Detached leaves of resistant/edited inbred (upper) and susceptible/non-edited inbred plants (lower). (Credit: Corteva.)

Gene editing could also be used to improve sustainability. For instance, it could be used to enhance roots' ability to grow deeper to access water or store more carbon in the soil, or it could change the oil composition of soy to replace crops such as palm, whose oil production often leads to deforestation.[56] It could also accelerate the adaptation of existing or new agricultural crops to grow in sustainable agricultural systems, such as enabling cover crops in row cropping systems, or altering the days a crop needs to mature. The technology can also be used to accelerate the development of varieties suited for indoor agriculture (focusing on quality, taste, and nutrition vs. resistance to environmental stress).

The possibilities and problems that gene editing could address for the benefit of agriculture, food production, and sustainability are plentiful. The utility and benefits are not limited to only certain crops or targets. Indeed, its use across agriculture will likely accelerate greatly over the next decade.

Deja Vu? Realizing the True Potential of Gene Editing for Agriculture

Gene editing is clearly a major breakthrough in the crop improvement. In many ways, we are at a similar juncture today with genome editing as we were with GMO development in late 1980s and early 1990s, when there was much excitement about the possibility of biotechnology in transforming agriculture. Today, we see a gene-editing landscape that is rich with entrepreneurial start-up energy as barriers to entry are significantly lower than GMO research. As a result, several new products are near commercialization, and the pace of new product development will only grow as more companies, organizations, and institutions invest in the technology.

As gene editing develops, it is important we learn from the history of past innovations and ensure its use balances the needs of agriculture and food production, societal acceptance, accessibility, and oversight. Now is the time to apply these learnings, as the applications, public perspectives, and regulatory oversight of the technology are nascent and evolving. We can learn from the social acceptance of transgenic technologies. Communication and transparency of gene-editing technology, its uses, technology accessibility, and a compelling value proposition are paramount to the conversation.

Transparency

Thirty-five years since their introduction, and despite abundant data on their safety, Americans are largely split on their views about the safety of GMOs. Just more than half of American adults believe GMOs are worse for people's health than foods with no GM ingredients.[57] Early efforts to promote the benefits of GMOs were hampered by a lack of public access to safety data. A 2016 report on the state of genetically engineered crops published by the National Academies states that "Transparency and public participation are critical [for trust]."[58] Because of its many positive attributes, gene editing presents a unique messaging and transparency opportunity for the scientific community.

In 2021, Corteva Agriscience unveiled a website dedicated to showing the technologies used in their products, as well as explanations of what these technologies are.[59] This transparency should help demystify current and emerging technologies shaping modern plant breeding, such as genome editing, for interested consumers. (For growers and partners in the food system, the site includes a complete Seed Product Directory of the corn, soy, canola, and sunflower products available in North America and Europe along with the breeding technologies used to create each variety.)

Genome editing technology accessibility

The CRISPR IP landscape is rich and evolving, including patents and patent applications from multiple parties for a variety of CRISPR-Cas enzymes. In 2017, Corteva (formerly DuPont Pioneer) and Broad Institute have developed a joint nonexclusive licensing framework for agricultural use that provides access to IP from Broad Institute co-owned with their collaborators, and nonexclusive access to foundational IP licensed by Corteva from Caribou Biosciences, ERS Genomics, and Vilnius University. To make CRISPR technology available to academic research community, Corteva Agriscience provides nonexclusive licenses at no cost to academic researchers and nonprofit organizations for noncommercial research use.[60] Furthermore, this IP is also licensed to for-profit agricultural companies for commercial use in their product development pipelines. This accessibility creates a rich and accessible innovation ecosystem, widening the pipeline of solutions being developed to improve crop production.

Gene-editing regulatory framework

Another critical element in the application of genome editing technologies in agriculture will be risk-proportionate and harmonized regulatory frameworks around the world. To date, there is no international regulatory framework for gene editing. Each nation is at a various stage of evaluating their guidelines.[61] Several countries have clarified their regulatory approach to gene editing by applying criteria if specific genome editing outcomes would meet the country's trigger for regulation, which, in many jurisdictions, is the creation of a GMO.

In 2019, a U.S. Presidential Executive Order directed federal agencies to streamline the regulatory process for genetically engineered plants. It also called for the creation of a single platform to clearly outline all regulatory requirements for review and authorization.[62] In 2020, the USDA reaffirmed its focus on regulating organisms based on their characteristics, as opposed to the process used to create them. The latter is currently the model used in the European Union (EU).[63]

The EU's approach to the legal and regulatory framework for GMOs is more precautionary in nature than that of the United States. Under this framework, products of conventional mutagenesis are considered GMOs but are exempt from GMO regulations. Gene editing is a targeted mutagenesis technique that can create organisms indistinguishable from organisms that could be developed with conventional mutagenesis or found in nature, although in a much more efficient and precise manner. However, in 2019, the European Court of Justice ruled that although such gene-edited organisms should be likewise considered GMOs under the law, they should not be exempt from GMO regulation, citing insufficient history of use of the technique. This decision creates a risk-disproportionate approach where like products are treated differently based solely on the technique with which they were produced.

Various stakeholders in the EU voiced deep concern with the court's decision, emphasizing that the EU regulatory system is risk-disproportionate and advocated for a legislative change. A comprehensive study by the European Commission was completed in April 2021 and concluded that the EU GMO legislation must adapt to scientific and technological progress. In September 2021, the European Commission began a series of consultations with stakeholders to frame an updated regulatory process by as early as 2024–2025. It will be incumbent upon plant breeders, researchers, public and private institutions, and nongovernmental organizations to advocate for a science-based approach to regulatory policies for gene-edited agricultural products in Europe, as well as around the world.

The adoption of GMO technology in the developing world, Asia and Africa lagged the developing world, primarily due to the slow establishment of regulatory frameworks within developing countries to approve cultivation of GMO crops. The developing world has much to benefit from the application of gene editing to issues such as malnutrition and climate adaptation. Although the regulatory status of gene editing has not yet been determined in any African country, South Africa has completed an expert report on the regulatory implications, and Kenya's National Biosafety Authority is drafting guidelines to regulate gene-edited products. Likewise, in Asia, India has established a tiered regulatory policy on gene editing, and China, although not yet issuing regulatory guidance, has invested >$10 billion in gene-edited research for the past 10 years, more than any other country globally. Therefore, it seems promising that the developing world will secure access to gene-editing products and technology more urgently than it did with GMO technology.[64]

Overall, there are many lessons that the scientific and business communities can apply to gaining public trust and acceptance of gene editing in the agricultural arena. Bringing in consumers, public, nongovernment organizations, regulators, and other stakeholders into the dialogue is critical to gaining awareness and trust.

So too is showcasing the potential that gene editing brings to such critical areas as climate change, food security, sustainable agriculture, and human and animal health. Making the technology available to everyone, everywhere helps create a sense of equality and democracy for the innovation. It is important, too, to show transparency and communicate what is coming in the innovation pipeline so that stakeholders understand the progression of these innovations and what they mean for society. And finally, it is critical that the science and business communities advocate for science-based regulations and articulate a constant drumbeat of science-based facts.

As members of the scientific community, we all have a major role in guiding this technology, not only from a technical standpoint but also through open robust communication with stakeholders, beneficiaries, and society. All of which could unlock its potential to be the next breakthrough technology in our 10,000-year journey of plant breeding. The time is now, for our actions will make history.

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References

1. Mendel G. Versuche über Plflanzen-Hybriden. In: Verhandlungen des naturforschenden Vereines in Brünn. Brünn: Im Verlage des Vereines,1866; pp. 3–47.
2. Chong JX, Buckingham K, Jhangiani S, et al. The genetic basis of Mendelian phenotypes: discoveries, challenges, and opportunities. *Am J Hum Genet.* 2015;97:199–215. DOI: 10.1016/j.ajhg.2015.06.009.
3. Lumpkin TA. How a gene from Japan revolutionized the world of wheat: CIMMYT's quest for combining genes to mitigate threats to global food security. In: *Advances in Wheat Genetics: From Genome to Field* (Ogihara Y, Takumi S, Handa H; eds.). Tokyo: Springer. 2015; pp. 13–20.
4. Scientific American. Norman Borlaug: Wheat Breeder Who Averted a Famine with a 'Green Revolution.' Available at https://blogs.scientificamerican.com/news-blog/norman-borlaug-wheat-breeder-who-av-2009-09-14/ Last accessed November 17, 2021.
5. National Science Foundation Office of Legislative and Public Affairs. First Ever Complete Plant Genome Sequence Announced. Available at https://www.nsf.gov/od/lpa/news/press/00/pr0094.htm Last accessed December 3, 2021.
6. Conrow J. New Study: GMO crops reduce pesticide use, greenhouse gas emissions. Available at https://allianceforscience.cornell.edu/blog/2020/07/new-study-gmo-crops-reduce-pesticide-use-greenhouse-gas-emissions/ Last accessed February 3, 2022.
7. U.S. Census Bureau. Quick Facts, Agriculture. Available at https://www.census.gov/quickfacts/fact/table/US/PST045219 Last accessed December 3, 2021.
8. Crop Life. Agriculture Then and Now. Available at https://croplife.org/news/agriculture-then-and-now/ Last accessed November 17, 2021.
9. World Health Organization. World Hunger Report. Available at https://www.who.int/news/item/15-07-2019-world-hunger-is-still-not-going-down-after-three-years-and-obesity-is-still-growing-un-report Last accessed November 12, 2021.
10. Ortiz-Bobea A, Ault TR, Carrillo CM, et al. Anthropogenic climate change has slowed global agricultural productivity growth. *Nat Clim Chang.* 2021;11:306–312. DOI: 10.1038/s41558-021-01000-1.
11. Kikkert JR, Vidal JR, Reisch BI. Stable transformation of plant cells by particle bombardment/biolistics. *Methods Mol Biol.* 2005;286:61–78. DOI: 10.1385/1-59259-827-7:061.
12. Gelvin SB. Plant DNA repair and Agrobacterium T-DNA integration. *Int J Mol Sci.* 2021;22:8458. DOI: 10.3390/ijms22168458.
13. Srivastava N, Gupta K, Pati R, et al. Genetically by modified crops: an Overview. *Biotechnology.* 2011;10: 136–148. DOI: 10.3923/biotech.2011.136.148.
14. Rasco-Gaunt S, Riley A, Cannell M, et al. Procedures allowing the transformation of a range of European elite wheat varieties via particle bombardment. *J Exp Bot.* 2001;357:865–874. DOI: 10.1093/jexbot/52.357.865.
15. Daniell H. Molecular strategies for gene containment in transgenic crops. *Nat Biotechnol.* 2002;20:581–586. DOI: 10.1038/nbt0602-581.
16. Anand A, Wu E, Li Z, et al. High efficiency Agrobacterium-mediated site-specific gene integration in maize utilizing the FLP-FRT recombination system. *Plant Biotechnol J.* 2019;17:1636–1645. DOI: 10.1111/pbi.13089.
17. Purdue University. Food Biotechnology. Available at https://www.four-h.purdue.edu/foods/Food%20biotechnology%20frame1.htm Last accessed December 3, 2021.
18. Padgette SR, Kolacz KH, Delannay X, et al. Development, identification, and characterization of a glyphosate-tolerant soybean line. *Crop Sci.* 1995;35:1451–1461. DOI: 10.2135/cropsci1995.0011183X003500050032x.
19. Round-Up Ready Xtend Crop Systems. Education Resources. Available at https://www.roundupreadyxtend.com/stewardship/educational-resources/pages/default.aspx Last accessed December 3, 2021.
20. Cornell University Alliance for Science. New Study: GMO Crops Reduce Pesticide Use, Greenhouse Gas Emissions. Available at https://allianceforscience.cornell.edu/blog/2020/07/new-study-gmo-crops-reduce-pesticide-use-greenhouse-gas-emissions/
21. Bijman J. AgBioForum. Agrevo: From Crop Protection to Crop Production. Available at https://agbioforum.org/agrevo-from-crop-protection-to-crop-production/ Last accessed December 3, 2021.
22. Nandula VK. Herbicide resistance traits in maize and soybean: current status and future outlook. *Plants.* 2019;9:337. DOI: 10.3390/plants8090337.
23. USDA Economic Research Service. Agricultural Survey. Available at https://www.ers.usda.gov/ Last accessed December 3, 2021.
24. ISAAA Brief 55-2019. Biotech Crops Drive Socio-Economic Development and Sustainable Environment in the New Frontier. Available at https://www.isaaa.org/resources/publications/briefs/55/executivesummary/default.asp Last accessed November 17, 2021.
25. Lyons J, Bruening G. New technologies are changing the face of agriculture. *Hilgardia.* 2000;54:4–6. DOI:10.3733/ca.v054n04p4.
26. Simmons CR, Lafitte HR, Reimann KS, et al. Successes and insights of an industry biotech program to enhance maize agronomic traits. *Plant Sci.* 2021;2007:110899. DOI: 10.1016/j.plantsci.2021.110899.
27. Wu J, Lawit SJ, Weers B, et al. Overexpression of zmm28 increases maize grain yield in the field. *Proc Natl Acad Sci.* 2019;116:23850–23858. DOI: 10.1073/pnas.1902593116.
28. Gonsalves D, Ferreira S, Manshardt R, et al. Transgenic virus resistant papaya: new hope for control of papaya ringspot virus in Hawaii. *APSnet (published online).* 2018. DOI: 10.1094/PHP-2000-0621-01-RV.
29. Singh V, Sing R, Kumar A. Food security and plant disease management. Sawston, UK: Woodhead Publishing. 2021.
30. Statement by the American Association for the Advancement of Science Board of Directors: Legally Mandating GM Food Labels Could "Mislead and Falsely Alarm Consumers. October 2012. Available at https://www.aaas.org/news/aaas-board-directors-legally-mandating-gm-food-labels-could-mislead-and-falsely-alarm Last accessed December 3, 2021.
31. CropLife International. A Consultancy Study for CropLife International, September 2011. Available at https://croplife.org/plant-biotechnology/regulatory-2/cost-of-bringing-a-biotech-crop-to-market/ Last accessed December 3, 2021.
32. Hill WG. Understanding and using quantitative genetic variation. *Biol Sci.* 2010;365:73–85. DOI:10.1098/rstb.2009.0203.
33. Yasui Y. History of the progressive development of genetic marker systems for common buckwheat. *Breed Sci.* 2020;70:13–18. DOI:10.1270/jsbbs.19075.
34. Melchinger AE, Lee M, Lamkey KR, et al. Genetic diversity for restriction fragment length polymorphisms: relation to estimated genetic effects in maize inbreds. *Crop Sci.* 1990;30:1033–1040. DOI: 10.2135/cropsci1990.0011183X003000050016x.
35. Williams JGK, Kubelik AR, Livak KJ, et al. DNA polymorphisms amplified by arbitrary primers are useful as genetic markers. *Nucleic Acids Res.* 1990;18:531–6535. DOI: 10.1093/nar/18.22.6531.
36. Vos P, Hogers R, Bleeker M, et al. AFLP: a new technique for DNA fingerprinting. *Nucleic Acids Res.* 1995;23:4407–4414. DOI: 10.1093/nar/23.21.4407.
37. Jenkins S, Gibson N. High-throughput SNP genotyping. *Comp Funct Genomics.* 2002;3:57–66. DOI: 10.1002/cfg.130.
38. Edwards SM, Buntjer JB, Jackson R, et al. The effects of training population design on genomic prediction accuracy in wheat. *Theor Appl Genet.* 2019;132:1943–1952. DOI: 10.1007/s00122-019-03327-y.

39. Bernardo R. Reinventing quantitative genetics for plant breeding: something old, something new, something borrowed, something BLUE. *Heredity.* 2020;125:375–385. DOI: 10.1038/s41437-020-0312-1.
40. Meuwissen T, van den Berg I, Goddard M. On the use of whole-genome sequence data for across-breed genomic prediction and fine-scale mapping of QTL. *Genet Sel Evol.* 2021;53:19. DOI: 10.1186/s12711-021-00607-4.
41. Nepolean T, Kaul J, Mukri G, et al. Genomics-enabled next-generation breeding approaches for developing system-specific drought tolerant hybrids in maize. *Front Plant Sci.* 2018;9:361. DOI: 10.3389/fpls.2018.00361.
42. Yoosefzadeh-Najafabadi M, Earl HJ, Tulpan D, et al. Application of machine learning algorithms in plant breeding: predicting yield from hyperspectral reflectance in soybean. *Front Plant Sci.* 2021;11:624273. DOI: 10.3389/fpls.2020.624273.
43. Eckerstorfer MF, Engelhard M, Heissenberger A, et al. Plants developed by new genetic modification techniques-comparison of existing regulatory frameworks in the EU and Non-EU countries. *Front Bioeng Biotechnol.* 2019;7:26. DOI: 10.3389/fbioe.2019.00026.
44. Xing HL, Dong L, Wang ZP, et al. A CRISPR/Cas9 toolkit for multiplex genome editing in plants. *BMC Plant Biol.* 2014;14:327. DOI: 10.1186/s12870-014-0327-y.
45. Jaganathan D, Ramasamy K, Sellamuthu G, et al. CRISPR for crop improvement: an update review. *Front Plant Sci.* 2018;985. DOI:10.3389/fpls.2018.00985.
46. Kawall K. New possibilities on the horizon: genome editing makes the whole genome accessible for changes. *Front Plant Sci.* 2019;10:525. DOI: 10.3389/fpls.2019.00525.
47. Zaidi S, Mahas A, Vanderschuren H, et al. Engineering crops of the future: CRISPR approaches to develop climate-resilient and disease-resistant plants. *Genome Biol.* 2020;21:289. DOI: 10.1186/s13059-020-02204-y.
48. Anzalone AV, Randolph PB, Davis JR, et al. Search-and-replace genome editing without double-strand breaks or donor DNA. *Nature.* 2019;576:149–157. https://doi.org/10.1038/s41586-019-1711-4.
49. Abdelrahman M, Wei Z, Rohila JS, et al. Multiplex genome-editing technologies for revolutionizing plant biology and crop improvement. *Front Plant Sci.* 2021;12:721203. DOI: 10.3389/fpls.2021.721203.
50. Batista-Silva W, da Fonseca-Pereira P, Martins AO, et al. Engineering improved photosynthesis in the era of synthetic biology. *Plant Commun.* 2020;1:100032. DOI: 10.1016/j.xplc.2020.100032.
51. Waltz E. GABA-enriched tomato is first CRISPR-edited food to enter market. *Nat Biotech.* 2021. Available at: https://www.nature.com/articles/d41587-021-00026-2 Last accessed January 11, 2022.
52. Newell-McGloughlin M. Nutritionally improved agricultural crops. *Plant Physiol.* 2008;147:939–953. DOI: 10.1104/pp.108.121947.
53. Do PT, Nguyen CX, Bui HT, et al. Demonstration of highly efficient dual gRNA CRISPR/Cas9 editing of the homeologous GmFAD2–1A and GmFAD2–1B genes to yield a high oleic, low linoleic and α-linolenic acid phenotype in soybean. *BMC Plant Biol.* 2019;19:311. DOI: 10.1186/s12870-019-1906-8.
54. Tshala-Katumbay DD. Cyanide and the human brain: perspectives from a model of food (cassava) poisoning. *Ann N Y Acad Sci.* 2016;1378:50–57. DOI: 10.1111/nyas.13159.
55. Raza A. Impact of climate change on crops adaptation and strategies to tackle its outcome: a review. *Plants.* 2019;8:34. DOI:10.3390/plants8020034.
56. Innovature: Nourishing Tomorrow. Gene Editing is a Key to Environmental Sustainability. Available at https://innovature.com/article/gene-editing-key-environmental-sustainability Last accessed December 3, 2021.
57. Pew Research Center. US Adults' Perceptions of GMOs. Available at https://www.pewresearch.org/fact-tank/2020/03/18/about-half-of-u-s-adults-are-wary-of-health-effects-of-genetically-modified-foods-but-many-also-see-advantages/ Last accessed December 3, 2021.
58. National Academies Press. Science Breakthroughs to Advance Food and Agriculture Research by 2030. Available at https://www.nap.edu/read/25059/chapter/1 Last accessed December 5, 2021.
59. Corteva Agriscience. Demystifying Modern Plant Breeding. Available at https://www.corteva.com/our-impact/transparency/plant-seed-transparency/demystifying-modern-plant-breeding.html Last accessed November 17, 2021.
60. International Rice Research Institute. IRRI Licenses CRISPR Technology from Broad Institute and Corteva Agriscience. Available at https://www.irri.org/irri-licenses-crispr-technology-broad-institute-and-corteva-agriscience Last accessed December 3, 2021.
61. Entine J, Felipe, MSS, Groenewald JH, et al. Regulatory approaches for genome edited agricultural plants in select countries and jurisdictions around the world. *Transgenic Res.* 2021;30:551–584 DOI: 10.1007/s11248-021-00257-8.
62. Genetic Literacy Project. Global Gene Editing Regulation Tracker. Available at https://crispr-gene-editing-regs-tracker.geneticliteracyproject.org/united-states-crops-food/ Last accessed December 3, 2021.
63. USDA. About The Secure Rule. Available at https://www.aphis.usda.gov/aphis/ourfocus/biotechnology/biotech-rule-revision/secure-rule/secure-about/340_2017_perdue_biotechreg Last accessed December 2, 2021.
64. Genetic Literacy Project. Global Gene Editing Regulation Tracker. Available at: https://crispr-gene-editing-regs-tracker.geneticliteracyproject.org/africa-crops-food/ Last accessed January 11, 2022.