ANNUAL REVIEWS

Annual Review of Phytopathology

Genome Editing, Gene Drives, and Synthetic Biology: Will They Contribute to Disease-Resistant Crops, and Who Will Benefit?

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Annu. Rev. Phytopathol. 2019. 57:8.1–8.24

The *Annual Review of Phytopathology* is online at phyto.annualreviews.org

https://doi.org/10.1146/annurev-phyto-080417-045954

Keywords

gene drives, gene editing, genetically engineered crops, science and society, social equity, synthetic biology

Abstract

Genetically engineered crops have been grown for more than 20 years, resulting in widespread albeit variable benefits for farmers and consumers. We review current, likely, and potential genetic engineering (GE) applications for the development of disease-resistant crop cultivars. Gene editing, gene drives, and synthetic biology offer novel opportunities to control viral, bacterial, and fungal pathogens, parasitic weeds, and insect vectors of plant pathogens. We conclude that there will be no shortage of GE applications to tackle disease resistance and other farmer and consumer priorities for agricultural crops. Beyond reviewing scientific prospects for genetically engineered crops, we address the social institutional forces that are commonly overlooked by biological scientists. Intellectual property regimes, technology regulatory frameworks, the balance of funding between public- and private-sector research, and advocacy by concerned civil society groups interact to define who uses which GE technologies, on which crops, and for the benefit of whom. Ensuring equitable access to the benefits of genetically engineered crops requires affirmative policies, targeted investments, and excellent science.

INTRODUCTION

In the earliest days of plant genetic engineering (GE), there was no shortage of enthusiasm and ambition to apply this exciting new technology to agriculture. One striking example of such a broad vision is seen in Barton & Brill (12), who foresaw GE targets for crop improvement: modified seed proteins to enhance nutritional value, nitrogen fixation to reduce use of nitrogen fertilizers, improved photosynthesis to increase productivity, and increased stress tolerance and pest and pathogen resistance to reduce crop losses and production costs and improve environmental safety. However, 36 years later, few of these dreams have come true. This may be in part because these dreams focused on humanitarian and environmental sustainability goals that were difficult to monetize, whereas those who commercialized genetically engineered crops had to turn a relatively quick profit while complying with complex and costly regulations. The early successes were mostly made by companies focused on simple traits for big markets, i.e., herbicide or insect resistance for major row crops. However, one small nonprofit team developed and commercialized the first pathogen-resistant perennial crop: the *Papaya ringspot virus* (PRSV)-resistant papaya (43), which was credited with saving the papaya industry in Hawaii. Yet, despite the obvious potential, in 2019 there are still few examples of pathogen-resistant genetically engineered crops on the market.

Several novel GE technologies are particularly exciting because they are relatively simple, accurate, and affordable to apply, making them useful to address challenges and opportunities for the crops of resource-poor farmers and underserved consumers (11, 151). Newer GE technologies, notably gene editing, are now reaching maturity and their social acceptance and regulatory protocols are still being forged (66). The US Department of Agriculture (USDA) determined in March 2018 that single-gene knockouts or single base-pair mutations via genome editing would not be regulated by the agency (137). Although this decision offered reason for optimism among those developing genetically engineered crops in the United States, the US Food and Drug Administration (FDA) and the US Environmental Protection Agency (EPA) rulings are yet to come (103). A precautionary approach to regulating products of gene editing was taken by the European Court of Justice in July 2018 (33), whereas a month later, the Japanese government ruling recommended that gene-edited plants without foreign nucleotides should not be regulated (138). Heavy commercial and academic research investments by China suggest no reticence to create or use gene-edited crops (23), whereas India is debating the issue (1). It is unknown how African and other societies will decide to regulate novel GE technologies.

Genetic engineering (GE): the introduction or change of DNA, RNA, or proteins by human manipulation to effect a change in an organism's genome or epigenome

In this review, we consider how GE technologies can contribute to crops that meet the challenges of provisioning the world with food, feed, fiber, medicines, aesthetics, ecological controls, and structural materials, with an emphasis on crop pathogen resistance. The world requires increasing agricultural production to meet food and feed demands of a growing population with rising incomes (3, 133). These demands coincide with growing awareness of the environmental footprint of agriculture and the need to adapt farming and consumer practices to ensure sustainability of production (115). Moreover, expected changes in global climate (64) will modify the range and severity of pest and disease outbreaks (15) and affect yields and yield stability (96).

The greatest burden of these converging challenges will fall on the poor, and especially the poor in tropical, net food-importing countries (13, 35). Therefore, we first explore the potential current and future benefits of genetically engineered crops, especially for controlling plant pathogens of crops that are staples or otherwise crucial to farmers and consumers in lower-income countries. Reflecting on the many factors beyond science and technology that complicate delivery and deployment of genetically engineered crops for plant protection, we then discuss social drivers, challenges, and opportunities affecting whether farmers and consumers, especially the poor or those in small markets or of minor crops, will benefit from them.

SCIENTIFIC OUTLOOK FOR GENETICALLY ENGINEERED DISEASE RESISTANCE IN CROPS

Gene Editing: Genetic Engineering Technology for Today and the Future

Several creative strategies have been used to achieve demonstrable plant resistance to pathogens through gene editing. Editing of plant genes that encode susceptibility factors or negative defense regulators can result in resistance to various pathogens (105). In rice (*Oryza sativa*), for example, transcription activator-like effector nucleases (TALENs) were used to mutate an effector-binding element in the *OsSWEET14* gene and render it nonsusceptible to activation by *Xanthomonas oryzae* pv. *oryzae* (*Xoo*) to acquire sugars for its nutritional needs (82). Analogous effects have been achieved for *Xanthomonas* on other hosts, e.g., cassava and cotton, and demonstrate useful levels of sequence conservation among host genes targeted by the pathogens (34). Naturally occurring mutations of eukaryotic translation initiation factors (*eIF4E* and *eIF4G*), mildew locus O (*MLO*), and *Xa5* and *Xa13* genes confer resistance to potyviruses, fungal pathogens, and bacterial pathogens, respectively, by depriving the pathogens of essential host factors (105, 127), and their effects can be replicated by gene editing to create point mutations and partial or complete gene deletions. Baltes et al. (9) demonstrated that the bacterial CRISPR-Cas immunity system can be adapted to protect plants from plant viruses by transforming plants to introduce the CRISPR-Cas reagents, loaded with guide RNA, which is complementary to sequences within multiple viral genomes. Finally, genome-incorporated CRISPR-Cas can be used in regulating gene transcription or to posttranscriptionally target RNA, thereby avoiding editing host genes that may have other essential functions (76).

Knott & Doudna (76) reviewed advances and prospects for using CRISPR-Cas technologies for genetically engineering diverse genomes, including those of plants. Many applications may require the transient or permanent incorporation of the CRISPR-Cas system into the recipient genome. Wang et al. (141) describe how transgenerational CRISPR-Cas9 activity can be used in plant breeding to modify multiple targets or in breeding crosses between lines with and without incorporated CRISPR-Cas9 constructs, both leading to nontransgenic final products. For improvement of clonal cultivars, e.g., cassava, transient expression or excision of a Cas nuclease may be preferred for limiting intended mutagenesis to a narrow timeframe and maximally maintaining the cultivar's unique genotype. Nonclonal crops may likewise benefit from using transgene-free genome editing methods (145) to increase precision and, potentially, decrease the regulatory burden.

In reviewing current methods, challenges, and opportunities in applied plant gene editing, Yin et al. (149) noted a great need for (*a*) nontransgenic CRISPR-Cas enzyme delivery mechanisms

CASSAVA BROWN STREAK DISEASE

Cassava (*Manihot esculenta*) is grown on more than 23 million ha across Africa, Asia, and Latin America and provides food and income for more than 800 million people (29). Cassava is the second most important staple crop after maize in sub-Saharan Africa, where 300 million people derive their livelihoods from its production and more than half of the population obtain 10–50% of their caloric intake from it (70, 131).

Cassava brown streak disease (CBSD) is a major emerging disease devastating cassava production in Uganda and the Democratic Republic of Congo and around Lake Tanganyika. Crop damage due to CBSD can reach 70%, and economic damages in Africa are estimated at US$75–100 million annually (88) or higher (95). Two distinct species of ipomoviruses belonging to the family *Potyviridae* cause CBSD (104) and are vectored by whitefly.

The Donald Danforth Plant Science Center in the United States and partners in Kenya, Nigeria, and Uganda lead the Virus Resistant Cassava for Africa project (132), which addresses the challenges of viral diseases as well as nutritional deficiencies in the storage roots. Stable and strong resistance to CBSD has been achieved using GE, and confined field trials have been conducted in Uganda and Kenya. Cassava with resistance to Cassava mosaic disease (CMD) is being conventionally crossed with the CBSD-resistant cassava obtained through GE. Materials produced by this project will be made available to partner countries royalty-free.

and (*b*) minimization and management of off-target edits. In terms of opportunities, advances in applying bioinformatics and machine learning to explore the growing number of sequenced plant genomes (29) will identify candidate genes or sequences for editing, including some that may achieve broad-spectrum resistance or tolerance to diverse plant pathogens. Some knowledge-based resistances may be applicable across hosts and pathogens, and their deployment across multiple crops will require strategies to maintain their effectiveness by minimizing selection pressure on the pathogens.

Case 1: Genetic Engineering Applications for Disease Control in Cassava

Cassava is an important crop for resource-poor farmers because it grows reasonably well on marginal soils, with unreliable rainfall, and with minimal inputs, and many varieties have a broad time window for harvest that allows staggered harvests to meet food and marketing needs (see the sidebar titled Cassava Brown Streak Disease). Cassava mosaic disease (CMD), caused by at least seven species of geminiviruses, cassava brown streak disease (CBSD), caused by two species of potyviruses, and cassava bacterial blight (CBB), caused by *Xanthomonas axonopodis* pv. *manihotis* (*Xam*), are widespread in Africa, and although several sources of resistance are known and used in breeding for CMD resistance, only weak or no sources of resistance are available for CBSD and CBB (11). Evidence suggests that the *CMD2* resistance gene is negatively regulated in wild-type cassava and that gene editing could stably mutate the negative regulator, making it unavailable for use by the virus for inactivating *CMD2* (11). Similar to the above-cited examples (82, 105, 127), targeted mutations of *eIF4E* and *MeSWEET10a* in cassava are attractive options for controlling the potyviruses that cause CBSD, and *Xam*, which causes CBB (11, 52).

Transgenic approaches have also been demonstrated or proposed to control CMD, CBB, and CBSD in cassava (see the sidebar titled Cassava Brown Streak Disease). The effectiveness of RNA interference (RNAi) in controlling *Cassava brown streak virus* (CBSV) and Ugandan CBSV has been demonstrated (17, 139), including partial control using artificial microRNA (amiRNA) (140). Chavarriaga-Aguirre et al. (29) proposed the use of RNAi to interfere with the ability of whitefly (*Bemisia tabaci*) to infect cassava and cause CMD or CBSD, but this approach has not been validated (see the section titled Case 4: Genetic Engineering Applications to Control Insect Vectors of Plant Disease Pathogens and the section titled Gene Drives: Incipient and Future Genetic Engineering Technology). Transformation of cassava with a bacterial resistance gene(s) from other species, modified to include an effector-binding element for *Xam* in their promoter region, could provide resistance to CBB; Hummel et al. (62) demonstrated this approach by adding a stack of effector-binding elements for three strains each of *Xoo* and *Xanthomonas oryzae* pv. *oryzicola* to the promoter region of rice's *Xa27* bacterial blight resistance gene.

Case 2: Genetic Engineering Applications to Control *Aspergillus* in Peanut

Aflatoxins are secondary metabolites produced by some fungi of the genus *Aspergillus*, especially *Aspergillus flavus* and *Aspergillus parasiticus*. Aflatoxins are known mutagens and teratogens that can lead to human health problems, including increased risk of liver and kidney cancer, a weakened immune system, and failure of infants to gain weight or height as expected (failure to thrive) (77). Aflatoxins are of global importance because they contaminate food crops, including cotton, maize, peanut (*Arachis hypogaea* L.), and some tree nuts. Peanuts are widely used in sub-Saharan Africa as a staple food because they are nutrient rich and provide an economical protein source (92). Human exposure also includes contaminated meat and dairy products from animals fed contaminated crops (77). Although aflatoxin food contamination occurs in both developed and developing countries, people in developing countries experience more exposure, often because of suboptimal processing, storage, and inspection as well as lack of education about the issue (36, 92).

Control of *Aspergillus* spp. requires multiple tactics during crop production, processing, and storage. *Aspergillus*-resistant cultivars are desirable for reducing contamination, but conventional breeding has not produced varieties with sufficient resistance to reduce aflatoxins to an acceptable level (122). Therefore, GE approaches may be needed to develop these varieties.

RNAi is an effective approach for pathogen control because genes in the critical pathways for initial infection or spread can be downregulated to prevent disease development in the host (87). Arias et al. (7) demonstrated that silencing of five genes (*aflS*, *alfR*, *aftC*, *pes1*, and *aflep*) involved in aflatoxin synthesis and accumulation provided resistance in peanut. Bhatnagar-Mathur et al. (18) proposed that overexpression of lipoxygenase (*LOX*) genes, which are involved in peanut response to infection by *A. parasiticus* (91, 126), has the potential to provide resistance to *Aspergillus* spp. Subsequently, overexpression of two plant-derived antifungal genes, *BjNPRI* from brown mustard (*Brassica juncea)* and *tgfd* from fenugreek (*Trigonella foenum-graecum*), resulted in *A. flavus*–resistant peanut (129). Sharma et al. (122) combined overexpression of antifungal defensin genes (*MSDef1* from *Medicago sativa* and *MSDef4.2* from *Medicago truncatula*) to reduce initial infection, with host-induced gene silencing (HIGS) of *aflM* and *aflP* genes in the aflatoxin biosynthetic pathway to inhibit aflatoxin production in peanut; some products had aflatoxin levels well below US and European Union (EU) limits.

Case 3: Genetic Engineering Applications to Control Parasitic *Striga* spp. Weeds in Staple Cereals

Members of the genus *Striga*, commonly known as witchweeds, are parasitic plants in the Orobanchaceae family that attack a number of monocot and dicot crop species, including maize, sorghum, pearl millet, and rice, all of which are staples for many resource-poor farmers. *Striga*-caused crop losses affect 56% of sorghum and millet and 15% of maize areas in sub-Saharan Africa (55). Of the 39 African countries producing upland rice, almost 80% have at least one *Striga* sp. capable of parasitizing rice, with an estimated economic loss of US$117 million per year (116).

Control of *Striga* spp. is difficult because their seeds remain dormant until a host is present and exudes a germination stimulant. After germination, *Striga* attaches to the host root and forms a haustorium, which allows the parasite to acquire nutrients and water. Neither traditional breeding nor weed management techniques have provided sufficient *Striga* control. Genetic engineering may provide solutions for *Striga* control but will likely require multiple approaches because *Striga* spp. are not host specific and crops vary in their responses. Genes responsible for the production of root exudates that stimulate seed germination, attachment, and haustorium development are potential targets for GE.

In sorghum, the mutant low-germination stimulant allele (*lgs*) provides resistance to *Striga* (111). The mutant allele alters the strigolactone biosynthetic pathway to reduce production of the *Striga* germination stimulant strigol (50). The mutation does not block the pathway, which would be detrimental to the host, but alters biosynthesis so that a nongermination stimulant strigolactone is exuded by the roots. Editing of the *LGS* gene in other host crops (e.g., maize) could produce resistant cultivars.

RNAi gene silencing in *Cuscuta pentagona* and *Triphysaria versicolor* was successful in preventing haustorial establishment and development on tobacco (2) and lettuce (134), respectively. In maize, de Framond et al. (37) found that RNAi was not sufficient to create *Striga* resistance, whereas Kirigia et al. (73) succeeded in silencing a gene in *Striga hermonthica* using viral-induced gene silencing (VIGS).

Advances toward producing reference genomes for parasitic species should enable greater use of GE techniques to alter genes involved with parasitism (144). Comparative transcriptome analyses identified many putative parasitism genes that were upregulated during haustoria development of three *Orobanchaceae* spp., including *Striga hermonthica* (147). Determining which genes to target to prevent or reduce attachment in *Striga* is ongoing, but there have been promising outcomes.

Case 4: Genetic Engineering Applications to Control Insect Vectors of Plant Disease Pathogens

Aphids, thrips, whiteflies, leafhoppers, planthoppers, and treehoppers are important vectors of plant-pathogenic bacteria and viruses (41, 45, 107). The damage from the vectored pathogens can be reduced by plant resistance to the pathogen developed through breeding as well as transgenic approaches (79, 150). Alternatively, suppression of the pathogens can be achieved by plant resistance to the insect vector.

Classical host plant resistance breeding aimed at vectors has had some success. The *Mi* gene in tomato confers resistance to some strains of aphid and whitefly vectors of plant viruses (98, 118). Although this gene provides significant resistance, the level varies with plant age and environment (117), and only some aphid strains are affected (59). It might be feasible to use genomics and gene editing to improve the expression and performance of the *Mi* gene. Several breeding programs have selected single and multiple genes for resistance to hemipteran vectors of viral pathogens of rice, but these pests have evolved adaptations to the resistance (40, 61). The problem of insect vectors of plant pathogens evolving resistance to naturally occurring resistance mechanisms is widespread (124, 148); thus, deployments of conventionally bred resistant cultivars should apply strategies that maintain their effectiveness.

The need for appropriate deployment strategies extends to recent GE approaches for resistance to insect vectors (130). Toxins from the bacterium *Bacillus thuringiensis* (Bt) have been successfully moved into a variety of crops to suppress damage from major lepidopteran and coleopteran pests (94). Efforts to modify the Bt toxin–coding genes to produce proteins that are toxic to Hemiptera have had limited success. Chougule et al. (30) were the first to develop a modified Bt toxin with some action against aphids. Subsequent efforts to modify another toxin-coding gene resulted in some improvements (113), but neither of these efforts resulted in commercial products. The Monsanto company also worked on developing Hemiptera-active Bt toxins and recently tested a plant-incorporated Bt aimed at control of *Lygus* plant bugs (8, 53). In addition to impacts on *Lygus*, these plants had significantly less damage from the *Frankliniella* species of thrips (53). It is feasible that this toxin could be used to control plant-pathogen vectors in the future.

Beyond the use of Bt toxins, researchers have been considering a number of other effector molecules that include spider-derived toxins expressed in phloem tissues and a lectin that could impact whiteflies and aphids (56). The use of plant-produced RNAi to control insect pests has been considered for a number of years (14), but only recently has strong insect control with this method been accomplished (152). Unfortunately, recent work has also shown that selection for resistance to a specific RNAi transcript can result in broad resistance to RNAi (71). Therefore, as with all forms of plant resistance to insect herbivores, RNAi approaches must follow strategies to maintain their effectiveness.

Gene Drives: Incipient and Future Genetic Engineering Technology

A strikingly different approach for suppressing populations of plant-pathogen vectors, or interfering with their transmission of plant pathogens, involves insect transgenesis with selfish genetic elements that cause super-Mendelian inheritance of insect traits that interfere with either insect reproduction or pathogen replication (51, 125). These gene drive approaches have progressed rapidly in the past few years (78). Approaches for engineering insects to suppress pathogen replication have also moved forward (39), but much work remains. It is likely that the first field releases of insects for disease control will focus on insects that transmit human pathogens, but this may open opportunities for using these approaches for suppression of specific insect-vectored plant pathogens. It is important to note that gene drive strategies are not feasible unless there is obligate sexual reproduction. Most aphids are therefore not targets for gene drives, and some pathogen-vectoring thrips can also be parthenogenic (68). *Bemisia tabaci* whiteflies are haplodiploid (26); thus, they could be targeted through the meiotic stage of females, but the process would not be as effective as it would be in the typically sexual, diploid planthoppers and leafhoppers (69). One current target of gene drives is the Asian citrus psyllid that transmits the pathogen involved in citrus greening (10). Neve (97) describes possibilities to apply CRISPR-Cas9-based gene drive systems for agricultural weed management, although overcoming the tremendous seed production capacity or the self-fertilizing nature of many weed species makes this challenging. The technologies used for gene drives are in their infancy but will likely mature into useful species-specific, geographically confinable, and recallable (89) tools for pest management.

Synthetic Biology: Unfolding and Futuristic Genetic Engineering Technology

Synthetic biology applies GE principles to design and alter natural systems or artificially construct biological devices and systems with predictable behaviors (83, 121). CRISPR-mediated gene editing is a synthetic biology extension of current GE paradigms and is already proving useful for conferring various resistance traits to crops. Looking beyond gene editing, the redesign of simple genetic parts, usually as single components in a construct, such as promoters, has been the most frequent embodiment of synthetic biology. At its core, synthetic biology should be capable of endowing extensive and transformative changes to organisms by leveraging advanced computational design and building synthetic DNA constructs and then large-scale installation of many genetic components into plant genomes at once or in series. Analogous to the DNA sequencing revolution that has enabled reading genomic DNA, the emerging DNA synthesis revolution allows for unprecedented scales of writing DNA into genomes.

In Sc2.0 (**http://syntheticyeast.org**), the most ambitious synthetic biology program with a eukaryotic organism to date, each chromosome of baker's yeast (*Saccharomyces cerevisiae*) is being synthesized and inserted into the genome piece by piece (24, 114). The goal is to create the first synthetic genome within a complex organism. This stepwise rebuilding of a complete genome elucidates an unprecedented understanding of the organism and its fundamental biology, raising immense prospects for rewriting genomes. Advances in synthetic biology may enable the design, building, and installation of a synthetic genome into plants (or even a chromosome or subgenome) to confer pest resistance or for other practical uses in agriculture. Indeed, writing large amounts of synthetic DNA into plants has natural precedence in the form of viruses, such as caulimovirus and geminivirus, that exist episomally and add information to plant genomes.

The most amenable subgenome in plants for synthetic engineering is the plastid genome, and the expanding list of crop plants with engineered plastids currently includes soybean, lettuce, and potato. Given that the plant kingdom excels in producing a wide range of biochemicals, it follows that the blueprints for endowing crops with new defense chemicals exist in nature. As one example, the plant kingdom knows how to produce more than 21,000 different alkaloids, including those with pesticidal properties (38, 123). Although technologically challenging at present, it should be feasible to identify the key gene(s) in metabolic pathways by which plants produce fungicidal compounds. In addition, it should also be feasible to transfer these genes into a crop where they would be inducibly expressed upon fungal infection.

A second, even more futuristic and transformative example, is the production and installation of a synthetic chloroplast genome, a synplastome (110), for broad pest resistance. We know that the plastid is the target of multiple viruses that cause disease in plants (153). Of all plant genomes, the plastome would be the most straightforward to design, build, and install, not least because it is minuscule compared with the nuclear genome (e.g., the tobacco plastome is only 156 kb and contains ∼100 genes). Although the first synplastome is nearing completion (110), we still do not know how difficult it will be to install and maintain a synplastome in plants as a replacement for the native plastome. If successful, it could enable large-scale metabolic engineering within the plastid itself.

One particularly intriguing idea is to recode the genome to endow resistance to viruses. Bacterial virus (bacteriophage) infection is a tremendous practical problem when using bacteria as bioreactors and in laboratory cultures. Although various recoding experiments have been performed, Ostrov et al. (100) conducted the most pertinent study to our review when she and colleagues removed seven codons from the *Escherichia coli* genome. The elimination of seven codons required more than 62,000 mutations, which rendered very few errors in the recoded genome. In addition, the cognate tRNAs for each of the six-amino-acid–deleted codons (there was one recoded stop codon) were deleted. This study is the latest effort to totally recode the *E. coli* genome for virus resistance. An earlier effort recoded a stop codon and achieved resistance to the T7 bacteriophage (80). Recoded genomes render the codons of invading viruses untranslatable in the host. For example, if a key viral stop codon is deleted in its host genome but recoded in the host to another stop codon, the virus cannot infect the host. Indeed, Ma & Isaacs (86) found that a stop codon–recoded *E. coli* was resistant to multiple viruses. A completely recoded plastome could, theoretically, result in complete and broad resistance against all plastid-targeted viruses because the viruses would no longer be able to replicate or express genes in the plastid. Scott Lenaghan (personal communication) has calculated that recoding histidine to use a single tRNA would require only 324 mutations in the plastome, which may be achievable through gene editing, although doing so would be an ambitious undertaking. A more radical approach, e.g., the reduction of a single codon each for histidine, tyrosine, and valine, would require 1,583 mutations, which may be possible only through a synplastomic approach. Synthetic genome biology could offer an evolutionary revolution by giving crops an advantage in the evolutionary race against much more nimbly evolving pathogens. Indeed, recoding codons may be a new integrative strategy for virus resistance. Doing so would set up viral roadblocks to multiple viruses, instead of the one-by-one resistance strategy that is currently common.

Summary: Genetic Engineering Science and Technology

The GE toolbox has expanded since its earliest days, and plant scientists are using these tools in the discovery, validation, and, increasingly, deployment of improved, including disease-resistant, crops. New and emerging GE tools appear to offer great potential, perhaps exceeding the largely unrealized vision of Barton & Brill (12) 36 years ago. Although conventional as well as twentieth- and twenty-first-century biotechnologies offer a variety of approaches to solve challenges in plant protection, it is critically important to understand and address prospective applications in relevant socioeconomic contexts, globally and locally, given that these affect the implementations, including by whom, for whom, and what, when, and where.

SOCIOECONOMIC CONTEXT INFLUENCING THE FUTURE OF GENETICALLY ENGINEERED CROPS

Many published analyses conclude that genetically engineered crops outyield and economically outperform their non–genetically engineered counterparts (see the sidebar titled Realized and Opportunity Benefits and Costs of Genetically Engineered Crops). Furthermore, as shown above, it is unlikely that there will be a shortage of GE innovations in the agricultural and life sciences. However, social–institutional contexts have shaped and will continue to shape the capacity of researchers to develop their ideas and the capacity of farmers to gain access to and realize the

REALIZED AND OPPORTUNITY BENEFITS AND COSTS OF GENETICALLY ENGINEERED CROPS

A report by the National Academies of Science, Engineering, and Medicine (NASEM) (94) and several recent meta-analyses conclude that genetically engineered maize, cotton, and soybean varieties often outyield and economically outperform their conventional counterparts (21, 42, 74, 106, 112). The yield advantage is greater for insect-resistant crops under conditions of substantial pest pressure than for herbicide-resistant crops. The advantages have been estimated as 14–40% greater in developing than in developed countries (6, 27, 42, 74). Economic benefits have generally accrued to farmers adopting transgenic crops (6, 22, 63, 74, 94, 106, 108). It is important to note that some of the studies cited here do not differentiate between yield increases caused by the transgene, differential farmer practices, and seed quality or differences between breeding efforts associated with genetically engineered and non–genetically engineered varieties (94).

Adoption or nonadoption of genetically engineered crop technologies has also resulted in opportunity benefits (63) and costs (20, 143) that are often overlooked. The wide use of genetically engineered insect-resistant crops can suppress a targeted insect(s) across broad regions and increase yield and economic benefits for adopters and nonadopters of the genetically engineered varieties (63). Unintended costs of adopting genetically engineered crops may also accrue, e.g., those caused by glyphosate-resistant weeds for US farmers (84, 90). However, this should be considered alongside the economic (94) and ecological benefits accrued from genetically engineered crops enabling the use of glyphosate instead of more toxic herbicides (75).

potential benefits from new technologies. Although we highlight the roles of social and institutional contexts, this does not deny the role of individuals' beliefs and values on the types of genetically engineered crops that are developed and deployed (94). Rather, it recognizes that understanding the institutional contexts helps to explain why stakeholders engage in one activity or adopt one position as opposed to another (58).

Beyond conferring disease resistance, enhanced yield, or improved agronomic performance, genetically engineered crops can contribute to societal ambitions to reduce pesticide use and chemical applications in general and agriculture's negative impacts on nontarget organisms and biodiversity. Genetically engineered crops, deployed within integrated systems, can contribute to disease and pest management within agroecologically sustainable boundaries (81, 94).

Institutional Factors Affecting the Realization of the Potential Benefits of Genetically Engineered Crops

Multiple institutional factors affect which traits and crops benefit from research investments that include the use of GE technologies. We review four factors that are relevant in both low- and high-income countries and discuss how they converge to determine who might benefit from genetically engineered crops.

Public-sector investments play a crucial role in genetic engineering and research and development outcomes. Various authors have documented large investments by the private sector in the United States on genetically engineered crops and other high-technology agricultural research. Concomitantly, however, public expenditures on agricultural research and development (R&D) in many high-income countries have stagnated and even begun to decline (60). Public-sector investments in R&D and in science and technology vary in low- and middle-income countries. Whereas China, India, and Brazil have greatly increased their public agricultural research capacity and agricultural output (60), public investments in R&D and science have generally plateaued or declined in sub-Saharan Africa (16, 146). Weak R&D capacity in many low-income nations, exacerbated by declining public-sector funding by high-income nations, raises concerns about many countries' abilities to develop and deliver high-quality innovations using GE and other complex technologies.

Most of the genetically engineered crops deregulated and approved for field release in the United States relate to herbicide and insect resistance in crops that are produced on large areas and offer good returns on investment in R&D (94). Apart from some traits that address pathogens in minor crops, including papaya, potato, plums, and squash, there are few GE applications related to plant diseases. In contrast to minor crops, which are produced in smaller areas, orphan crops, such as yam, are important staples and widely grown in many lower-income nations. Orphan crops may attract little private-sector investment because they are grown primarily by resource-poor households with little capacity to purchase inputs such as genetically engineered seeds or vegetative material. As a result, most research on minor and orphan crops has been funded through the public purse and conducted by universities and international research centers.

During the first decade of genetically engineered crop research at universities in the United States, research agendas increasingly shifted toward major crops and away from minor crops, thus looking more like private-firm research agendas (142). Two interconnected socioeconomic trends help to explain this shift. The first is that public funding for agricultural R&D in the United States remained flat from the 1980s to the early 2000s and declined in subsequent decades. Second, investments by the private sector increased significantly, especially in biological sciences. These trends resulted in a dramatic increase in the private share of agricultural and food R&D

investments while driving the public sector to increase its focus on major crops and pursue income-generating opportunities (see below) to close the funding gap (48). Pressures to increase private returns from university R&D cut across all agricultural research efforts in US universities. Incidentally, Barton & Brill (12) repeatedly emphasized the need for more basic research on plant biochemistry as a prerequisite for achieving the potential benefits from genetically engineered crops that they envisioned 36 years ago. Perhaps the excitement of success with simple engineered traits has contributed to insufficient funding for this basic research.

High benefit-to-cost ratios for US federal and state investments, estimated at 10:1 to 30:1, signal underinvestment in agricultural R&D, which even at 10:1 imposes a net social cost of at least US$36 billion per year (4, 5). To help resolve such drastic underinvestment, Pardey & Beddow (102) proposed doubling US public investment in agricultural R&D as a first step, followed by regular and sustained increases in the long run. Development and delivery of the potential benefits of genetically engineered crops to smallholder farmers in lower-income countries require the extension of the recommendation to the public international research system conducting R&D in and for lower-income countries.

Intellectual property regimes influence genetic engineering and research and development outcomes. Another important trend in the United States and elsewhere is that crops are increasingly protected by intellectual property (IP) rights, including utility patents (146). The 1930 Plant Patent Act and the 1970 Plant Variety Protection Act (PVPA) in the United States and the International Convention for the Protection of New Varieties of Plants (UPOV), allowed for the protection of plants that are deemed "distinct, uniform, and stable" (19). Although the PVPA and UPOV protected new varieties, they allowed scientists to conduct research and develop innovations on those protected varieties, and farmers could save seed for replanting but not sale.

By contrast, utility patents prevent farmers from saving seed for replanting and scientists from conducting research or developing innovations on patented crops without the approval of the patent holder (94). The United States began allowing the application of utility patents to crops generated through biotechnology in the 1980s and extended this to include conventionally bred crops in 2001. In contrast, the European Union prohibits patents on biological processes, which include crossing and selection by breeders.

There are two competing narratives regarding IP. A more pessimistic narrative describes IP regimes as detrimental to innovation, especially to the development of public goods, and proposes that IP instruments be limited in, if not withdrawn from, public policy. In the more positive narrative, IP regimes, despite providing time-limited market power to the grantee, promote innovation by protecting the IP of firms and individuals, helping them to secure returns on R&D investments. Resolving the detrimental versus incentive nature of IP regimes is directly related to whether private-sector R&D is a complement to or a substitute for public-sector R&D. Public policy introducing stronger IP regimes is viewed as an option to promote private investments in R&D and therefore can strongly influence the scope and beneficiaries of GE and overall agricultural R&D, especially in low-income countries (93).

The converging trends of a rising share of private R&D funding and the emergence of stricter IP protections are important because they indicate a shift in public policy toward the private sector in resolving agricultural problems. An area of concern is that the private sector is likely to invest mainly in major crops and major traits, so work on minor, perennial, clonal, or staple food crops of lower-income nations is likely to suffer. If not addressed, this will be a critical constraint on emerging technologies, including those addressing diseases, and especially in, but not limited to, low-income countries.

Biosafety regulatory issues influence genetic engineering and research and development outcomes. The costs and complexity of compliance with biosafety regulatory requirements can constrain genetically engineered crop R&D and deployment (94). The cost of regulatory compliance for transgenic crop varieties varies and may be as low as US$1.5–5 million for a small private firm in the United States or international research center in eastern Africa submitting a regulatory dossier for commercial release in just one country (94, 120). This contrasts with an estimate of US$35 million for regulatory approval of a transgenic crop variety following the industry standard for commercial crops requiring commercial release in at least two countries plus import approval of that crop for food and feed purposes in at least five countries (109).

The complex and potentially costly nature of complying with biosafety regulations may strongly influence which institutions undertake GE R&D and therefore which traits and crops are studied. As discussed above, many countries are still deciding whether and how they will regulate products of novel breeding technologies, with obvious consequences for the availability of potential benefits of these genetically engineered crops for their farmers and consumers (151).

Civil society institutions influence genetic engineering and research and development outcomes. Genetically engineered crops have been in commercial use in the United States since 1995, but their deployment and use in Europe remains limited. This difference is at least partially due to deep divisions in societal opinion concerning the risks and benefits of GE and to very vocal lobbying by environmental nongovernmental organizations (NGOs) and political parties. The risks of GE technologies include unintended effects, e.g., off-target editing, and unanticipated costs, such as herbicide-resistant weeds (the sidebar titled Realized and Opportunity Benefits and Costs of Genetically Engineered Crops describes examples of beneficial and negative unintended effects of genetically engineered crops). Potential risks from careless stewardship or misuse of some GE technologies require appropriate regulations and expert oversight (101). None of these risks is unique to GE technologies.

Graff et al. (54) argue that resistance from diverse stakeholders should be viewed within a political–economic context. They suggest that because US biotechnology firms were far ahead of firms in other countries in researching and commercializing genetically engineered crops, large agricultural chemical firms in Europe perceived a threat to their business model. Therefore, whereas large firms in the United States were commercializing and promoting genetically engineered crops, large European agricultural firms were not as advanced as the US firms and saw potential business risks to opening the European markets to the new technology. This created the political–economic space in Europe for consumer and small farmer advocacy groups to have greater influence on policy makers.

The influence of various concerned groups is perhaps exemplified by international protests such as the "March Against Monsanto," which has been an annual event across many countries since 2013 (**https://en.wikipedia.org/wiki/March_Against_Monsanto**). Essentially, the arguments against GE technologies have become conflated with arguments against the monopolies and oligopolies of the seed industry. Currently, five companies dominate more than 75% of global seed sales and all have major stakes in sales of agrochemicals, some of which are connected to genetically engineered crops.

Some objectors perceive that these firms are privatizing public goods such as genetic resources while increasing dependence on agrochemicals. The use of genetically engineered crops is prohibited in organic agriculture and strongly resisted by many promoting agroecology as a social movement. Thus, discussions about the use of GE technologies have become inextricably connected to debates about public–private ownership and access to genetic resources, the right of farmers to retain seed, food sovereignty, and the agroecological sustainability of food systems.

POTENTIAL BENEFITS OF GENETICALLY ENGINEERED LATE BLIGHT–RESISTANT POTATO

Giller et al. (46) discuss the role of GE in pest and disease management in relation to agroecology using the example of *cis*-gene engineered resistance to *Phytophthora infestans* (late blight) in potato. This GE technology was developed using public funds, with open public consultation throughout the process and patents taken out to prevent private monopoly of the resistance methods. The stacking of three sources of disease resistance within the same variety cut the required spraying of fungicides to a single spray, reducing costs and pressure on the pathogen to evolve fungicide resistance compared to the current practice of spraying 15–20 times per season.

This is a clear example of the tools of nature being harnessed to overcome an economically devastating disease with massive environmental benefits in terms of reduced fungicide use. Thus, GE is potentially one of the strongest tools for reducing dependence on agrochemicals and as such could be considered a fundamental agroecological approach (46). Genetically engineered crop technologies need to be evaluated on an individual trait basis, and their likely benefits or costs considered, free from dogmatic or ideological stances.

Convergence of institutional forces affects the realization of benefits from genetically engineered crop technologies. The research, development, and introduction of genetically engineered crops in the United States roughly coincided with the rise of a policy agenda directed at reducing public expenditures on agricultural R&D (49). Decreases in public investments on agricultural R&D cannot be blamed exclusively on genetically engineered crops because the United Kingdom and other countries in the EU have also cut public expenditures and sought to privatize R&D (44). However, Busch (25) suggests that policy makers may view innovations such as genetically engineered crops, which can be privatized more easily than previous products of agricultural crops, as a mechanism for reducing the role of government in agriculture.

The convergence of the reduction of public expenditures with a greater reliance on the private sector in the United States to conduct research and deliver outputs has been associated with a decline in agricultural research innovations (49) and university research on minor crops and minor traits (142) and consolidation of the seed industry (47). Concerns over real and perceived consequences of these trends have fueled social reactions, including some that focus on the role of GE technologies while ignoring or negating their potential benefits. For example, late blight–resistant genetically engineered potato, which would greatly reduce fungicide use (see the sidebar titled Potential Benefits of Genetically Engineered Late Blight–Resistant Potato), offers ecological benefits.

Realizing broad social and ecological benefits from GE technologies requires new approaches that counter current institutional convergence trends (**Figure 1**). New approaches require greater integration with agroecological perspectives and far more consideration of the social and institutional contexts within which GE research is conducted and its outputs are diffused. Substantial public-sector investments are necessary to deliver effective and trustworthy public-interest GE research and regulations. New plant breeding technologies, e.g., genome editing, can also help balance agricultural R&D efforts between large commercial crops and smaller or orphan crops and counter current trends toward concentration of the seed market into a few, large companies (151).

The Role of the International Public Research Systems in Genetically Engineered Crops Research

CGIAR (formerly known as the Consultative Group for International Agricultural Research, a global partnership of 15 public, nonprofit, agricultural R&D centers) and other national and

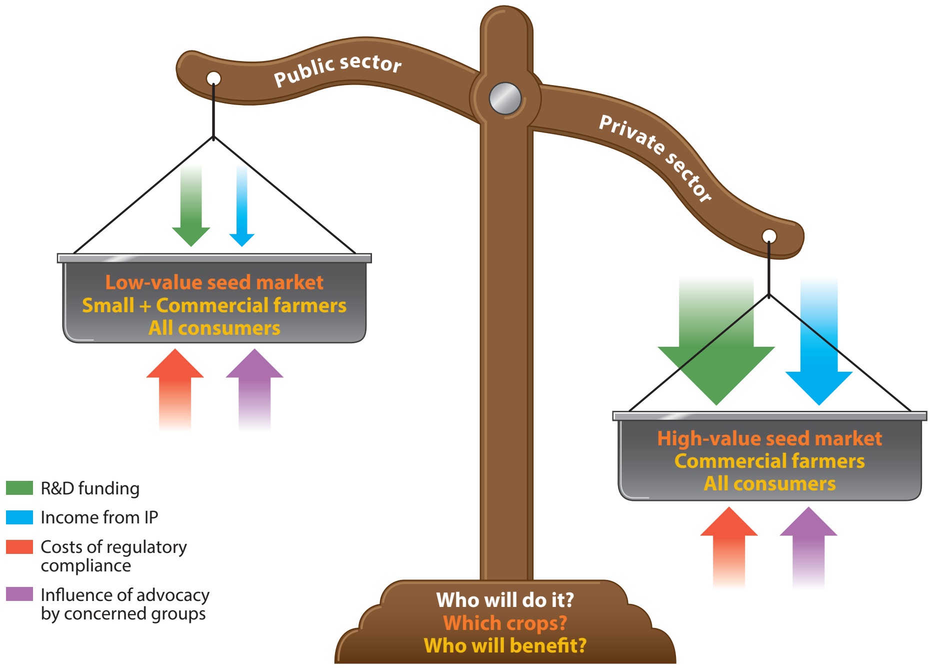

Figure 1

Institutional forces (*arrows*) alter the balance of (*a*) research and development (R&D) investments by the public relative to the private sector, (*b*) R&D emphasis on crops with low-value relative to high-value seed markets, which are often the crops of resource-poor versus resource-wealthy farmers, and therefore (*c*) who will benefit from the technologies as consumers of the improved crops. Achieving equity in access to the potential benefits of genetically engineered crops (or any technology, e.g., internet, cell phones, or radio) may require policy changes and actions (forces) to counterbalance prevailing trends. Figure created by Nancy Valtierra, CIMMYT.

international research centers have been at the forefront of generating public goods in agriculture and technologies for low-income countries. Although they do conduct R&D in genetically engineered crops, CGIAR centers have not taken a leadership position on them. GE research at nine CGIAR centers addresses tolerance to disease pathogens, insects, nematodes, drought, heat, flooding, salinity, and low soil nitrogen, as well as several nutritional and agronomic properties (**Supplemental Table 1**). This research involves banana, barley, bean, cassava, chickpea, cowpea, enset, groundnut, lentil, maize, pigeon pea, plantain, potato, rice, sorghum, sweet potato, and wheat (67, 99). The crops and traits are of interest to producers in low-income countries. Although several CGIAR genetically engineered crop projects are in the R&D pipeline, none have yet resulted in releases to farmers.

The relatively minor investment of CGIAR in GE research may be a consequence of institutional convergence forces described above. The complex IP environment surrounding GE technologies presents challenges to all small and medium-sized institutions (67), including the need to invest in regulatory capacity and expertise to research, develop, and deploy genetically engineered crops. Moreover, many CGIAR institutes work within the centers of diversity of the crops, which often implies that there are restrictions in terms of biosafety, germplasm use, and biodiversity, which may constrain GE R&D and innovation (67). Their funders, some of which are based in countries with a historical precautionary approach to genetically engineered crops and other advanced biotechnology techniques, also influence the CGIAR research agenda (72). Many of these challenges open reputational, financial, and liability concerns, even when following globally accepted standards.

Considering the critical role of CGIAR and other international and national agricultural research organizations in ensuring equitable access to technology, and that technology itself contributes to equitable impacts on society through productivity improvements, these public institutions are ethically compelled to assume a role in GE research. The International Maize and Wheat Improvement Center (CIMMYT) has issued public position statements explaining its rationale and guiding principles for conducting GE research (31, 32). Although the private sector does not share this specific mandate with the public sector, it can contribute to the public good through private–public collaborations.

The Bottom Line: Genetically Engineered Crops Reaching Farmers

Perhaps the best summary indicator of the opportunities and challenges presented by genetically engineered crops is the number and range of crops reaching farmers. The International Service for the Acquisition of Agri-Biotechnology Applications (ISAAA) (65) and Center for Environmental Risk Assessment (CERA) (28) databases list 497 crop varieties with genetically engineered traits that have been approved for commercial cultivation or importation as food or feed commodities, 22 of which pertain to disease resistance (**Table 1**). Crops in which disease resistance has been introduced using GE techniques include bean, papaya, plum, potato, squash, sweet pepper, and

Table 1 Crops, developer types, and target pathogens for genetically engineered disease tolerance traits approved for commercialization by 2018[a]

Crop	Number of events	Developer type	Descriptive commercial trait	Target pathogen	Country of initial approval for food, feed, and/or cultivation
Beans	1	Public	VR	*Bean golden mosaic virus* (BGMV)	Brazil
Papaya	2	Public	VR	*Papaya ringspot virus* (PRSV)	United States
	1	Public	VR	PRSV	China
Plum	1	Public	VR	*Plum pox virus* (PPV)	United States
Potato	3	Private	VR/IR	*Potato virus Y* (PVY)	United States
	3	Private	VR/IR	*Potato leaf roll virus* (PLRV)	United States
	4	Private	VR/HR	PLRV	United States
	3	Private	FR/PQ	Potato late blight (*Phytophthora infestans*)	Canada
Squash	1	Private	VR	*Zucchini yellow mosaic potyvirus* (ZYMV)/*Watermelon mosaic potyvirus 2* (WMV2)	United States
	1	Private	VR	*Cucumber mosaic cucumovirus* (CMV)/ ZYMV/ WMV2	Canada
Sweet pepper	1	Public	VR	CMV	China
Tomato	1	Public	VR	CMV	China

[a]Extracted from ISAAA GM Crop Approval Database (65) and CERA GM Crop database (28).

Abbreviations: FR, fungal resistance; HR, herbicide resistance; IR, insect resistance; PQ, product/agronomic quality; VR, viral resistance.

Table 2 Genetically engineered crop traits at various stages of regulatory approval in six African countries as of December 2017[a]

Country	BR	VR	FR	PQ	DT	IR	HR	AP	Stacked[b]	Other	Totals
Ghana	NA	0	0	0	0	1	0	1	0	0	2
Kenya	NA	3	1	1	0	2	NA	1	1	1	10
Malawi	NA	2	0	0	0	2	0	0	0	0	4
Nigeria	NA	0	0	1	0	2	0	2	1	0	6
Tanzania	NA	1	0	0	0	1	0	0	1	0	3
Uganda	2	2	0	1	1	1	1	1	1	0	10
Totals	2	8	1	3	1	9	1	5	4	1	35

[a]Compiled by authors from national biosafety authorities' reports and presentations, the Biosafety Clearing-House, and personal interviews.
[b]Stacked includes two DT/IR maize events in Kenya and Tanzania, one IR/HR maize in Nigeria, and one AP/DT rice in Uganda.

Abbreviations: AP, agronomic properties; BR, bacterial resistance; DT, drought tolerance; FR, fungal resistance; HR, herbicide resistance; IR, insect resistance; NA, not available; PQ, product/agronomic quality; VR, viral resistance.

tomato. Approvals for commercialization have been granted in Brazil, Canada, China, and the United States, and approvals for importation as food or feed (not listed in **Table 1**) have been made in a significantly larger number of countries.

Table 2 lists 35 genetically engineered crop products under consideration in seven African countries (see **Supplemental Table 2** for further details). These products are in crops of interest to smallholder farmers, including cassava, cowpea, sorghum, bananas, and maize. In this list, 11 of the 35 products are for disease resistance, outnumbering insect resistance and herbicide resistance, which have been the two traits with the largest share of releases globally. Furthermore, 23 are in the confined field trial stage, whereas 10 of the 35 are at the multilocational or general release (national performance) trial stage, indicating they could soon be available to farmers. The country with the most regulatory experience in Africa is the Republic of South Africa, with 21 commercially released genetically engineered cultivars of cotton, maize, and soybean (57) (**Supplemental Table 3**).

It is important not to assume that new crop technologies will inexorably become available to farmers as soon as the regulatory requirements are met or removed. Substantial investments are needed to use the new technologies to develop local varieties, generate necessary information and educational materials, explain the potential benefits and proper handling to farmers, produce enough seeds to meet farmer demands, and distribute the seeds to the farmers who want them. Furthermore, many smallholder farmers face social, economic, and gender barriers in getting access to the inputs, land, and labor needed to grow crops.

To realize the potential benefits of GE or other technologies requires defining and addressing the most important institutional constraints (136). For example, Traore (135) found that Guinean farmers in 2017 lacked access to improved conventional rice varieties since 2008 because of cutbacks in seed production and distribution infrastructure. Where important constraints already exist to spreading conventionally improved crop seeds, it is unlikely that genetically engineered crop seeds will be distributed more effectively unless appropriate resources and approaches are applied to address both existing and additional institutional constraints that apply to genetically engineered crops.

CONCLUSION

Disease control in agricultural crops will continue to have a significant role in addressing issues of food security and sustainability globally (119, 128), perhaps increasingly so with pending climate change (85). The already realized positive impacts on farm productivity and profitability, and the potential benefits from current, emerging, and future GE technologies are exciting, although nobody would propose that they are sufficient to ensure food security. We have described some notable examples of promising GE approaches to manage cassava viruses and bacterial blight, mycotoxin-producing fungi in groundnut, parasitic weeds in cereals, and insect vectors of plant-pathogenic bacteria and viruses, and we listed numerous emerging and potential other examples. To date, however, few genetically engineered crops addressing plant diseases have been released to farmers.

There are legitimate reasons why so few pathogen-resistant genetically engineered crops exist. Regulatory hurdles favor single-gene answers to pathogen resistance, but other than virus resistance, it is hard to find monogenic resistance. Nonetheless, the growing list of regulatory approvals of pathogen-resistant crops and the robust pipeline of emerging and future possibilities suggest that the greatest challenges will be nonscientific. Potent institutional forces will markedly influence whether and which benefits of genetically engineered crops are realized and by whom. Realizing the potential contributions of genetically engineered crops will require investments and policies in research, IP regimes, and regulatory frameworks while also addressing legitimate societal concerns about their responsible stewardship, agroecological sustainability, and equitable access to their benefits.

DISCLOSURE STATEMENT

K.V.P. is a co-principal investigator on a grant from the Bill & Melinda Gates Foundation to conduct gene editing for tolerance to maize lethal necrosis; he is also Director of the CIMMYT Genetic Resources Program, with oversight of biotechnology activities. K.E.G. is a member of the Sustainable Sourcing Advisory Board of Unilever. C.A.M.S. has received funding from agrochemical companies that commercialize genetically engineered crops. C.N.S. performs research and holds patents in plant biotechnology synthetic biology; the University of Tennessee Research Foundation is the signee of patents on which C.N.S. is an inventor. The University of Tennessee Institute of Agriculture receives grants and contract funds from government and private funders of plant biotechnology and synthetic biology that support research performed in C.N.S.'s laboratory at the university. J.F.Z. is a co-principal investigator on a grant from the Bill & Melinda Gates Foundation that supports economic assessments of genetically engineered technologies and provides policy support leading to functional biosafety systems in five countries in Africa; he also leads the economic policy group in a grant from the US Agency for International Development supporting the development of functional biosafety systems in Africa and Asia. All authors were coauthors of a National Academies of Science, Engineering, and Math report on genetically engineered crops (94) and might be perceived as having developed their perspectives on the use of genetically engineered crops for pathogen resistance prior to participating in the writing of the current review.

ACKNOWLEDGMENTS

K.V.P.'s contribution to this review was funded by the CGIAR research programs MAIZE and WHEAT. J.F.Z.'s contribution was funded by the BioRAPP project, which is cofunded by the Bill & Melinda Gates Foundation, the US Agency for International Development, and the CGIAR Research Program on Policies, Institutions, and Markets. Any opinions, findings, conclusions, or recommendations expressed in this publication are those of the authors and do not necessarily reflect the views of their employer institutions or funders.

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