



# Application of Gene Editing for Climate Change in Agriculture

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Climate change imposes a severe threat to agricultural systems, food security, and human nutrition. Meanwhile, efforts in crop and livestock gene editing have been undertaken to improve performance across a range of traits. Many of the targeted phenotypes include attributes that could be beneficial for climate change adaptation. Here, we present examples of emerging gene editing applications and research initiatives that are aimed at the improvement of crops and livestock in response to climate change, and discuss technical limitations and opportunities therein. While only few applications of gene editing have been translated to agricultural production thus far, numerous studies in research settings have demonstrated the potential for potent applications to address climate change in the near future.

**Keywords:** gene edited crops, livestock genetics, climate change, agriculture, food system, food security, livestock genetic resources, crop biotechnology

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## INTRODUCTION

Climate change poses a severe threat to the future of the environment as it pertains to agriculture, biodiversity, human society, and nearly every facet of our world. The primary cause of climate change is the anthropogenic addition of greenhouse gases to the atmosphere. Due to these human emissions, the average temperature of the planet has risen by nearly 1°C since 1850 (IPCC, 2018; Nunez et al., 2019). Even if warming were to be halted at 1.5°C, which would require drastic and immediate global action, long-term effects of past emissions would linger for centuries or millennia (IPCC, 2018). The magnitude of the effects depends on the amount of emissions; in general, more frequent heatwaves, droughts, floods, and persistent sea level rise and global temperature increases are expected (IPCC, 2018). Indeed, many of these effects are already being observed (IPCC, 2018; Nunez et al., 2019; Shukla et al., in press).

In both natural ecosystems and agricultural settings, plants and animals are being forced to contend with novel conditions that change more quickly than their pace of adaptation. Rising temperatures and shifting precipitation regimes will drastically alter the biological landscape, resulting in species migration, invasion, and extinction (Urban, 2015; Nunez et al., 2019). One meta-review of more than 130 studies has estimated that one in six species may go extinct due to the changing climate (Urban, 2015). Simultaneously, global food supplies are declining as droughts and floods impact agricultural output. Under a range of warming scenarios, agricultural output is expected to decline globally. Productivity of major commodity crops will be affected, especially in lower latitudes where the effects of climate change on yield will be more severe (Shukla et al., in press).

In response to these challenges, the use of gene editing, also referred to as genome editing or genome engineering, has emerged as a method to either aid in the adaptation of organisms to climate change or help mitigate the effects of climate change on agriculture.

Gene editing is a method to generate DNA modifications at precise genomic locations. These modifications can result in knockout or knockdown of one or multiple genes without the permanent insertion of any foreign DNA. Alternatively, genes from within the organism's genepool or from other organisms can be inserted into precise locations within the genome to knock-in a new trait. Transcription activator-like effector nucleases (TALENs), Zinc Finger Nucleases (ZFNs), and CRISPR/Cas systems have all been utilized to achieve precise gene edits (Gaj et al., 2016; Khalil, 2020). The precision and efficiency of generating edits has been tremendously improved by the introduction of CRISPR/Cas systems, although there is certainly still a role for other gene editing technologies. The application of gene editing techniques has generated great potential for developing crops and livestock that can better manage the impositions of climate change.

We seek here to illuminate the ways in which gene editing may help combat the deleterious effects of climate change by highlighting current efforts to apply these techniques in crops and livestock. We will summarize the efforts undertaken thus far and describe the limitations and opportunities that exist with gene editing technologies. **Tables 1–4**, provided at the end of the review, summarizes the breadth of applications of gene editing in crops and livestock.

## Climate Change Will Inhibit Agricultural Productivity

The effects of climate change have already started to emerge and will undoubtedly worsen. Currently, crops in lower latitude regions have begun to experience yield declines, while higher-latitude regions have experienced an increase in yield (Iizumi et al., 2018; Shukla et al., in press). However, global declines in yield and crop suitability are projected over the course of the century as a direct result of climate change. According to the Intergovernmental Panel on Climate Change (IPCC), extreme weather events will disrupt and decrease global food supply and drive higher food prices (Shukla et al., in press). In dry areas of the planet especially, climate change and desertification are likely to reduce agricultural productivity. Areas closer to the equator will be most vulnerable to declines in crop yield as temperature increases, with the continents of Asia and Africa having the largest populations vulnerable to increased desertification. Indeed, desertification has already started to reduce agricultural productivity and biodiversity, compounded by unsustainable land management and increased population pressure. While it is unclear to what extent aridity will increase on a global scale, it is likely that the area at risk of salinization will increase. Climate change will also contribute to current land degradation with increased droughts, floods, rising seas, and more intense tropical storms (Shukla et al., in press).

## Effects of Climate Change on Crops

The major contributing greenhouse gas to climate change is carbon dioxide (CO<sub>2</sub>) (IPCC, 2018; Shukla et al., in press), which generally has a positive effect on plant growth. As CO<sub>2</sub> concentration increases, so too does the rate of photosynthesis and carbon assimilation (an effect known as CO<sub>2</sub> fertilization) (Wang et al., 2020). Simultaneously, however, the nutritional quality of food decreases in response to heightened CO<sub>2</sub> (Shukla et al., in press). Furthermore, the increased growth associated with higher CO<sub>2</sub> may be offset by other environmental factors; there has been an observed decline in this CO<sub>2</sub> fertilization effect in the past 30 years, likely due to shifting nutrient concentrations and lower availability of water (Wang et al., 2020). Given the aforementioned increase in extreme temperature and precipitation events, combined with the shifting prevalence and range of diseases across the globe (Fisher et al., 2012; Bett et al., 2017), the overall effect of climate change on crops will be detrimental (Iizumi et al., 2018; Shukla et al., in press). Already, global yields of maize, wheat, and soybeans have slightly decreased from 1981 to 2010 relative to the pre-industrial climate (Iizumi et al., 2018).

## Effects of Climate Change on Livestock

Livestock will similarly be negatively affected by climate change. Increasing temperature and shifting precipitation directly impact livestock themselves, the crops grown for their feed, and diseases that infect them (Rojas-Downing et al., 2017; Shukla et al., in press). Increasing temperatures will have perhaps the most profound effects on livestock: heat stress impacts feed intake and can reduce weight gain, decreases reproductive efficiency, has multiple negative health effects, and increases mortality in many livestock species (Rojas-Downing et al., 2017).

## Climate Change Impacts Biodiversity and Food Systems

Beyond agriculture, the effects of climate change on biodiversity are no less severe. A recent meta-review of 97 studies found that even with only moderate increases of global temperature, biodiversity will suffer significant declines (Nunez et al., 2019). The pressures of climate change on biodiversity, in combination with increased agricultural demand, have also served to exacerbate the oftentimes antagonistic relationship between agricultural and natural landscapes. The impact of individual climate change effects and their intersections are complex. Broadly, the direct and indirect consequences of climate change will be deleterious to plant and animal performance in cultivated systems (**Figure 1**).

Mitigating the deleterious impacts of climate change on biodiversity is paramount. However, most applications of gene editing have converged on agricultural commodities: there are very few instances of gene editing for climate change in non-commodity organisms. This review therefore focuses on how gene editing solutions can address the broad effects of climate change on agriculture while maintaining the importance of applying these transformative technologies to the totality of biodiversity threatened by climate change.

**TABLE 1** | Summary of gene-editing applications for abiotic stress.

Species	Trait category	Trait targeted	Gene(s) Edited*	Method	Year published	References
Banana	Abiotic stress	Semi-dwarfed	Ma04g15900 Ma06g27710 Ma08g32850 Ma11g10500 Ma11g17210	CRISPR/Cas9	2019	(Shao et al., 2020)
Maize	Abiotic stress	Drought tolerance	ARGOS8	CRISPR/Cas9	2016	(Shi et al., 2017)
Rice	Abiotic stress	Drought Tolerance	EPFL9	CRISPR/Cas9, CRISPR/Cpf1	2017	(Yin et al., 2017)
Rice	Abiotic stress	Early flowering	Hd2, Hd4, Hd5	CRISPR/Cas9	2017	(Li et al., 2017)
Rice	Abiotic stress	Salt tolerance	OsRR22	CRISPR/Cas9	2019	(Zhang A. et al., 2019)
Cattle	Abiotic stress	Thermotolerance	SLICK	CRISPR/Cas9	2018	(Bellini, 2018)

## APPLICATIONS OF GENE EDITING IN AGRICULTURE

Here we present an extensive exploration of gene editing-based solutions in response to the daunting limitations to agricultural productivity imposed by climate change. We note that these examples are mostly from public institutions and represent proof-of-concept experiments rather than commercialized technologies.

### Increasing Abiotic Stress Tolerance

Abiotic stresses, including but not limited to drought, salinity, and flooding, pose some of the most severe threats to agricultural productivity in the face of climate change. Abiotic stress is anticipated to become more severe in agricultural systems as a result of climate change. Current research efforts demonstrate that gene editing is an effective tool in broadening resistance of crop tolerance as described in the following examples (Table 1, Figure 2).

### Salinity Tolerance in Rice

Rice, a staple food for more than half of the world's population, is of primary importance for global food security (Chauhan et al., 2017). Two major abiotic stresses that affect rice are drought and salinity, necessitating research explorations into the potential of leveraging gene editing for developing tolerant varieties. One such exploration was the use of CRISPR/Cas9 to knockout OsRR22, a gene associated with salt susceptibility in rice (Zhang A. et al., 2019). Rice plant performance in high salinity environments (0.75% NaCl) was improved with no concomitant decreases in grain yield, plant biomass, or grain quality. Edited lines were on average 19% shorter in saline solution whereas wild type plants were 32% shorter. Edited plants also had much less severe biomass reductions due to salt exposure compared to unedited plants, and showed no significant differences to unedited plants in the absence of saline. Saline studies were conducted in the greenhouse and overall agronomic performance was evaluated in the field. Researchers found that edited plants had much less severe biomass reductions due to salt exposure compared to wild type plants (Zhang A. et al., 2019).

### Drought Tolerance in Rice

Rice has also been engineered to improve drought and high temperature tolerance by targeting stomatal development. Stomata, which are anatomical features on the surface of all crop plant tissues, serve as the major sites of water loss. In this study researchers targeted a positive regulator of stomatal density in rice (Yin et al., 2017); while they did not explicitly test the effects of this editing on water use efficiency, other research has shown that stomatal reductions in rice have clear, positive implications for water use efficiency (Caine et al., 2019). Rice lines with reductions in stomatal densities had better yield in severe drought and were able to maintain lower temperatures despite no differences in yield. Stomatal density reductions achieved by a cisgenic approach in this case mirrored stomatal density reductions achieved by a knockout-based, gene-editing approach. Thus, reducing stomatal densities by gene-editing or cisgenic approaches could enable plants to resist water deficits and could also increase heat tolerance.

### Enabling Northern Production of Rice

An additional editing effort in rice produced early maturing rice that is more amenable to production in northern latitudes (Li et al., 2017). Northern latitudes experience longer day lengths and cooler temperatures. Applications of CRISPR/Cas9 to the flowering related genes Hd2,4 and 5, generated rice plants that flowered significantly earlier than their wild-type counterparts, making them more fit for northern production. These varieties may be well-suited for use in future conditions where temperatures and other climatic conditions near equatorial regions render farmlands less fertile. Early flowering plants may also be a useful adaptation against water deficit: by shortening the life span of crops through early flowering, less cumulative water may be required.

### Semi-dwarf Banana Varieties

In banana, gene editing using CRISPR/Cas9 to generate knockouts of genes for the biosynthesis of gibberellins has facilitated the development of a semi-dwarfed variety. This variety may be more resistant to lodging as a result of intense winds, typhoons, and storms, anticipated to increase in severity as a result of climate change (Shao et al., 2020). Semi-dwarfed varieties have historically been an important trait in crop

**TABLE 2** | Summary of gene-editing applications for disease tolerance.

Species	Trait category	Trait targeted	Gene(s) Edited*	Method	Year published	References
Banana	Disease	Banana streak virus	eBSV	CRISPR/Cas9	2019	(Tripathi J. N. et al., 2019)
Barley	Disease	Broad spectrum	MORC1	CRISPR/Cas9	2018	(Kumar et al., 2018)
Cacao	Disease	Resistance to phytophthora	TcNPR3	CRISPR/Cas9	2018	(Fister et al., 2018)
Cassava	Disease	Cassava brown streak disease	ncbp1/2	CRISPR/Cas9	2019	(Gomez et al., 2019)
Cotton	Disease	<i>Verticillium dahliae</i>	Gh14-3-3d	CRISPR/Cas9	2018	(Zhang Z. et al., 2018)
Cucumber	Disease	Broad spectrum viral resistance	elF4e	CRISPR/Cas9	2016	(Chandrasekaran et al., 2016)
Grape	Disease	Powdery mildew	VvMLO3	CRISPR/Cas9	2020	(Wan et al., 2020)
Grapefruit	Disease	Citrus canker	CsLOB1 promoter; CsLOB	CRISPR/Cas9	2016, 2017	(Jia et al., 2016, 2017)
Potato	Disease	Potato virus Y	Coilin C-terminal	CRISPR/Cas9	2019	(Makhotenko et al., 2019)
Rice	Disease	Bacterial blight resistance	OsSWEET 14 promoter; OsSWEET11 promoter; OsSWEET13	CRISPR/Cas9	2013, 2015	(Jiang et al., 2013; Zhou et al., 2015)
Rice	Disease	Rice leaf blast resistance	OsERF922	CRISPR/Cas9	2016	(Wang et al., 2016)
Rice	Disease	Powdery mildew	TaEDR1	CRISPR/Cas9	2017	(Zhang et al., 2017)
Rice	Disease	Broad spectrum	bsr-k1	CRISPR/Cas9	2017,2018	(Kumar et al., 2018; Zhou X. et al., 2018)
Rice	Disease	Rice tungro spherical virus	elF4G	CRISPR/Cas9	2018	(Macovei et al., 2018)
Rice	Disease	Bacterial blight	SWEET11, 13,14 promoters	TALENs	2019	(Xu et al., 2019)
Rice	Disease	Bacterial blight	SWEET11,13,14 promoters	CRISPR/Cas9	2019	(Oliva et al., 2019)
Rice	Disease	Bacterial blight	Os8N3	CRISPR/Cas9	2019	(Kim et al., 2019)
Tomato	Disease	Broad spectrum	SIDMR6	CRISPR/Cas9	2016	(de Toledo Thomazella et al., 2016)
Tomato	Disease	Powdery mildew	SIMLO1	CRISPR/Cas9	2017	(Nekrasov et al., 2017)
Tomato	Disease	Tomato yellow leaf curl virus	Coat and replicase protein of TYCV	CRISPR/Cas9	2018	(Tashkandi et al., 2018)
Tomato	Disease	Bacterial speck	SIJAZ2	CRISPR/Cas9	2018	(Ortigosa et al., 2019)
Wheat	Disease	Powdery mildew	TaMLOs	TALENs, CRISPR/Cas9	2014	(Wang et al., 2014)
Cattle	Disease	Mastitis	Lysostaphin, hLYZ	ZFN	2013, 2014	(Liu et al., 2013, 2014)
Cattle	Disease	Tuberculosis	SP110	TALE nickase	2015	(Wu et al., 2015)
Cattle	Disease	Leukotoxin resistance	CD18	ZFN	2016	(Shanthalingam et al., 2016)
Cattle	Disease	Tuberculosis	NRAMP1	CRISPR/Cas9	2017	(Gao et al., 2017)
Chicken	Disease	Avian leukosis	chNHE1	CRISPR/Cas9	2020	(Koslov et al., 2020)
Grass Carp	Disease	Grass carp reovirus	gcJAM-A	CRISPR/Cas9	2018	(Ma et al., 2018)
Pig	Disease	Porcine Respiratory Syndrome Virus, innate immunity	CD163, CD1D	CRISPR/Cas9	2014	(Whitworth et al., 2014)
Pig	Disease	Porcine respiratory syndrome virus	CD163	CRISPR/Cas9	2016	(Whitworth et al., 2016)
Pig	Disease	Porcine respiratory syndrome virus	CD163	CRISPR/Cas9	2017	(Burkard et al., 2017, 2018)
Pig	Disease	Classical swine fever	shRNA knock-in to <i>Rosa26</i> locus	CRISPR/Cas9	2018	(Xie et al., 2018)
Pig	Disease, nutrition	Classical swine fever, <i>fat-1</i>	<i>fat-1</i> knock-in to <i>Rosa26</i> locus	CRISPR/Cas9	2018	(Li M. et al., 2018)
Pig	Disease	Transmissible gastroenteritis virus	ANPEP	CRISPR/Cas9	2019	(Whitworth et al., 2019)

**TABLE 3** | Summary of gene-editing applications for land sparing.

Species	Trait category	Trait targeted	Gene(s) Edited*	Method	Year published	References
Maize	Land sparing	Yield	Waxy	CRISPR/Cas9	2020	(Gao et al., 2020)
Tomato	Land sparing	Yield	SICLV3, -S, -SP;	CRISPR/Cas9	2017	(Huang et al., 2018)
Ground Cherry	Land sparing; Nutrition	Highly nutritive crop modified for improved agronomic properties	Ppr -AGO7, -SP, -SP5g	CRISPR/Cas9	2018	(Lemmon et al., 2018)
Tomato	Land sparing, nutrition	Yield; Lycopene accumulation	SP, Multiflora, Ovate, Fasciated, Fruit Weight 2.2, Lycopene Beta Cyclase	CRISPR/Cas9	2018	(Zsögön et al., 2018)
Rice	Land sparing	Yield	DEP1, Gn1A	CRISPR/Cas9	2018	(Huang et al., 2018)
Rice	Land sparing	Yield	PYL 1,4,6	CRISPR/Cas9	2018	(Miao et al., 2018)
Rice	Land sparing	Yield	OsGs3, OsGW2, OsGn1A	CRISPR/Cas9	2019	(Zhou et al., 2019)
Wheat	Land sparing	Yield	GW2, LPX-1,MLO	CRISPR/Cas9	2018	(Wang et al., 2018)
Blunt snout sea bream	Land sparing	Yield	mstna, mstnb	CRISPR/Cas9	2020	(Sun et al., 2020)
Carp	Land sparing	Yield	sp7, MSTN	CRISPR/Cas9	2016	(Zhong et al., 2016)
Catfish	Land sparing	Yield	MSTN	CRISPR/Cas9	2017	(Khalil et al., 2017)
Cattle	Land Sparing	Yield	MSTN	ZFN, TALENs	2014, 2015	(Luo et al., 2014; Proudfoot et al., 2015)
Chicken	Land sparing	Yield	GOS2	CRISPR/Cas9	2019	(Park et al., 2019)
Chicken	Land sparing	Sex-determination	Fluorescent protein into sex chromosome	CRISPR/Cas9	2019	(Lee et al., 2019)
Goat	Land sparing	Yield	MSTN, FGF5	CRISPR/Cas9	2015	(Wang X. et al., 2015)
Goat	Land Sparing	Yield	MSTN	TALENs, CRISPR/Cas9	2016, 2016, 2018	(Ni et al., 2014; Guo et al., 2016; Yu et al., 2016; He et al., 2018)
Goat	Land sparing	Litter size	GDF9	CRISPR/Cas9	2018	(Niu et al., 2018)
Goat	Land sparing, disease	Yield	Fat-1 into MSTN	CRISPR/Cas9	2018	(Zhang J. et al., 2018)
Oyster	Land sparing	Yield	MSTN	CRISPR/Cas9	2019	(Yu et al., 2019)
Pig	Land sparing	Yield	MSTN	TALENs, ZFN, CRISPR/Cas9	2016, 2018, 2015, 2016, 2016, 2017	(Qian et al., 2015; Wang K. et al., 2015; Bi et al., 2016; Rao et al., 2016; Tanihara et al., 2016; Wang et al., 2017)
Pig, Buffalo	Land sparing	Yield	MSTN	CRISPR/Cas9	2018	(Su et al., 2018a)
Pig	Land sparing	Yield	IGF2	CRISPR/Cas9	2018, 2019	(Xiang et al., 2018; Liu et al., 2019)
Pig	Land sparing	Yield	FBXO40	CRISPR/Cas9	2018	(Zou Y. et al., 2018)
Rabbit	Land sparing	Yield	MSTN	CRISPR/Cas9	2016	(Guo et al., 2016)
Red sea bream	Land sparing	Yield	MSTN	CRISPR/Cas9	2018	(Kishimoto et al., 2018)
Sheep	Land sparing	Yield	MSTN	CRISPR/Cas9, TALENs	2015, 2014, 2015, 2016, 2019	(Han et al., 2014; Crispo et al., 2015; Proudfoot et al., 2015; Li et al., 2016; Zhang Y. et al., 2019)
Yellow catfish	Land sparing	Yield	MSTN	ZFN	2011	(Dong et al., 2011)

improvement, as was the case with rice and wheat that enabled the Green Revolution (Khush, 1999).

## Promoter Editing for Drought Tolerance in Maize

Beyond generating knockouts, gene editing tools can also facilitate knock-ins. Researchers have used CRISPR/Cas9 to insert a promoter at a specific maize locus to increase drought

tolerance (Shi et al., 2017). Specifically, an alternate maize promoter was inserted before ARGOS8, a gene associated with drought tolerance. This precise insertion enabled greater grain yield during flowering water stress, while maintaining yields in normal growth conditions. This approach represents an intragenic technique facilitated by gene-editing in which a native maize genetic sequence was introduced at a new locus to increase plant adaptation to an abiotic stressor.

**TABLE 4** | Summary of gene-editing applications for nutrition.

Species	Trait category	Trait targeted	Gene(s) Edited*	Method	Year published	References
Banana	Nutrition	Increased beta-carotene	LCY $\epsilon$	CRISPR/Cas9	2020	(Kaur et al., 2020)
Brassica napus	Nutrition	Increased oleic acid content	FAD2	CRISPR/Cas9	2018	(Okuzaki et al., 2018)
Camelina sativa	Nutrition	Reductions of linoleic acid and linolenic acid	FAD2	CRISPR/Cas9	2017, 2017	(Jiang et al., 2017; Morineau et al., 2017)
Cassava	Nutrition	Reduced starch	PTST1, GBSS	CRISPR/Cas9	2018	(Bull et al., 2018)
Maize	Nutrition	Reduced phytate levels	IPK1	ZFN	2009	(Shukla et al., 2009)
Maize	Nutrition	Reduced phytic acid	ZmPDS, ZmIPK1, ZmIPK, ZmMRP4	TALENs, CRISPR/Cas9	2014	(Liang et al., 2014)
Peanut	Nutrition	Increased oleic acid content	FAD2	TALENs	2018	(Wen et al., 2018)
Potato	Nutrition	Reduced starch	GBSS	CRISPR/Cas9	2017	(Andersson et al., 2017)
Rice	Nutrition	Increased amylose	SBEI, SBEIIb	CRISPR/Cas9	2017	(Sun et al., 2017)
Rice	Nutrition	Prevented cadmium uptake	OsNramp5	CRISPR/Cas9	2017	(Tang L. et al., 2017)
Rice	Nutrition	Increased carotenoids	GR-1 & GR-2 carotenoid biosynthesis cassettes inserted in GSHs	CRISPR/Cas9	2020	(Dong et al., 2020)
Sorghum	Nutrition	Reduced kafirins	K1C genes	CRISPR/Cas9	2018	(Li et al., 2018)
Soybean	Nutrition	Altered oil levels	FAD2-1A, FAD2-1B, FAD3A	TALENs	2016	(Demorest et al., 2016)
Strawberry	Nutrition	Altered sugar content	FvebZIPs1.1	CRISPR/Cas9	2020	(Xing et al., 2020)
Tomato	Nutrition	Increased anthocyanin levels	ANT1, PSY1	TALENs; CRISPR/Cas9	2015	(Cermák et al., 2015; Filler Hayut et al., 2017; Deng et al., 2018)
Wheat	Nutrition	Low gluten wheat for reduced allergenicity	Alpha-gliadin array, Gli-2 locus	CRISPR/Cas9	2018	(Sánchez-León et al., 2018)
Cattle	Nutrition	Reduction of milk allergen	BLG	ZFN	2011	(Yu et al., 2011)
Cattle	Nutrition	Reduction of milk allergen	LacS	TALENs	2018	(Su et al., 2018b)
Chicken	Nutrition	Less abdominal fat deposition	G0S2	CRISPR/Cas9	2018	(Park et al., 2019)

## Enhancing Thermotolerance of Cattle

In animals, gene editing has also been applied to mitigate abiotic stress imposed by climate change. Acceligen, a subsidiary of Recombinetics Inc., has undertaken an initiative to improve the thermotolerance of cattle, with support from the Foundation for Food and Agriculture Research (FFAR) and Semex. Researchers are focused on replicating the SLICK phenotype originally identified in Senepol cattle through gene editing. Variations of this phenotype in cattle contribute to thermotolerance (Dikmen et al., 2014; Porto-Neto et al., 2018). Conventionally bred cattle possessing SLICK genetics are more thermotolerant, as exhibited by lower vaginal temperatures, lower rectal temperatures, lower respiration rates, and more sweating, thus leading to increased milk production during summer months (Dikmen et al., 2014). Using gene editing approaches, Acceligen seeks to replicate SLICK genetics, to improve thermotolerance of important cattle breeds (Bellini, 2018).

## MANAGING DISEASE

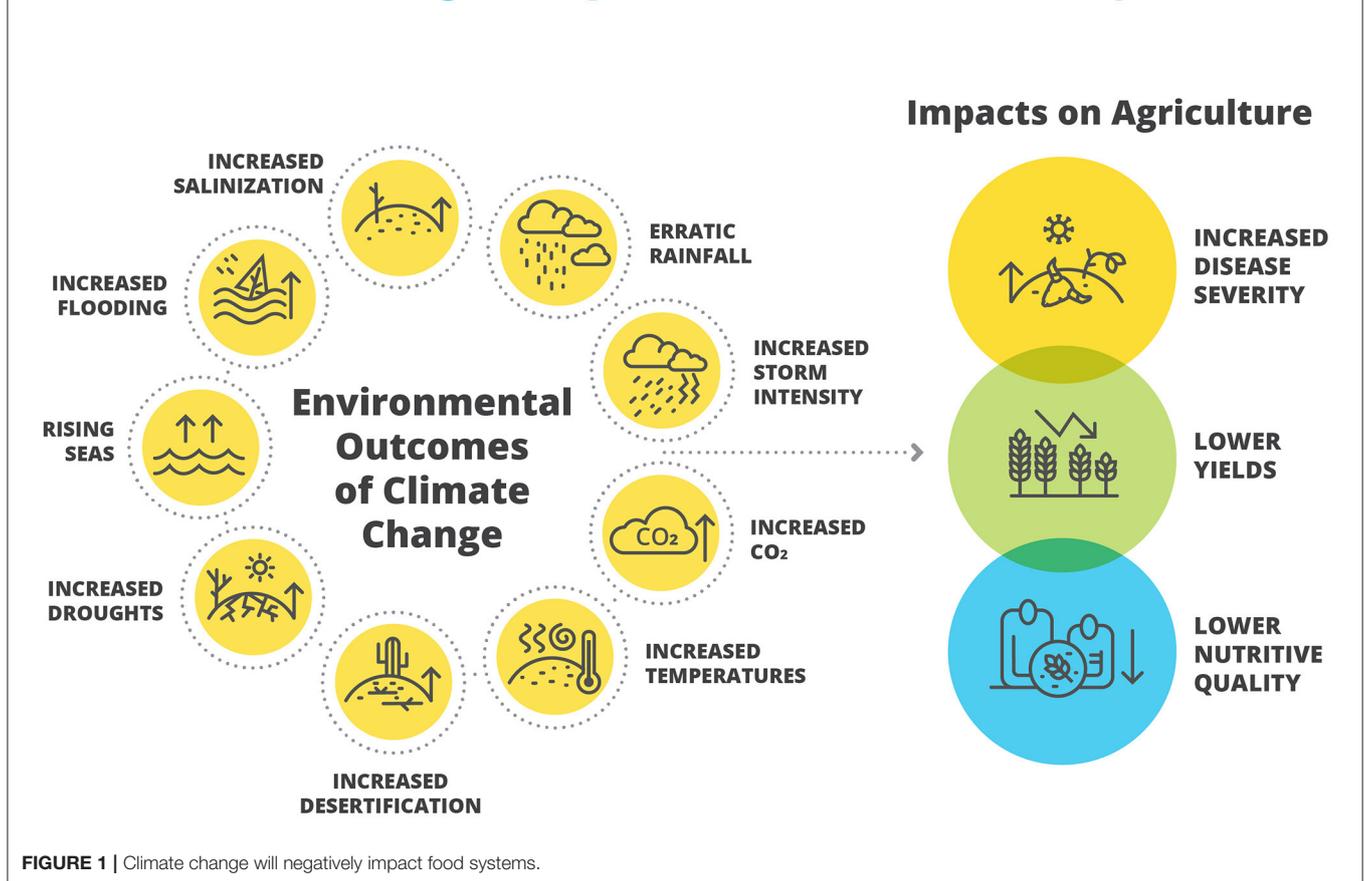
A majority of diseases affecting plants and animals are anticipated to become more widespread with climate change (Madgwick et al., 2011; Fisher et al., 2012; Bebbler, 2015; Bett et al., 2017;

Tang X. et al., 2017; Yan et al., 2017). Fortunately, many current gene editing efforts have shown promise in conferring disease resistance. This work will become even more necessary in coming years as climate change increases disease severity and incidence. Increased range of vectors, rising temperatures fostering reproduction of pathogens, and host organisms becoming more susceptible to pathogens are some of many climate change driven causes of worsening disease. Gene editing can provide a solution to managing these current and emerging global threats to agricultural productivity precipitated by climate change (Table 2, Figure 2).

## Plant Gene Editing for Disease Resistance

In plants, genes have been identified that increase disease resistance when knocked out. Altering genetic elements involved in susceptibility has thus far been the primary form of disease mitigation through gene editing. While there are few such genes available for increasing disease resistance, researchers have already successfully leveraged many of these loci for heightened resistance. The following examples demonstrate the effectiveness of knocking-out susceptibility loci for enhanced resistance.

# Climate Change Impacts on the Food System



## Increased Rice Resistance to a Range of Disease

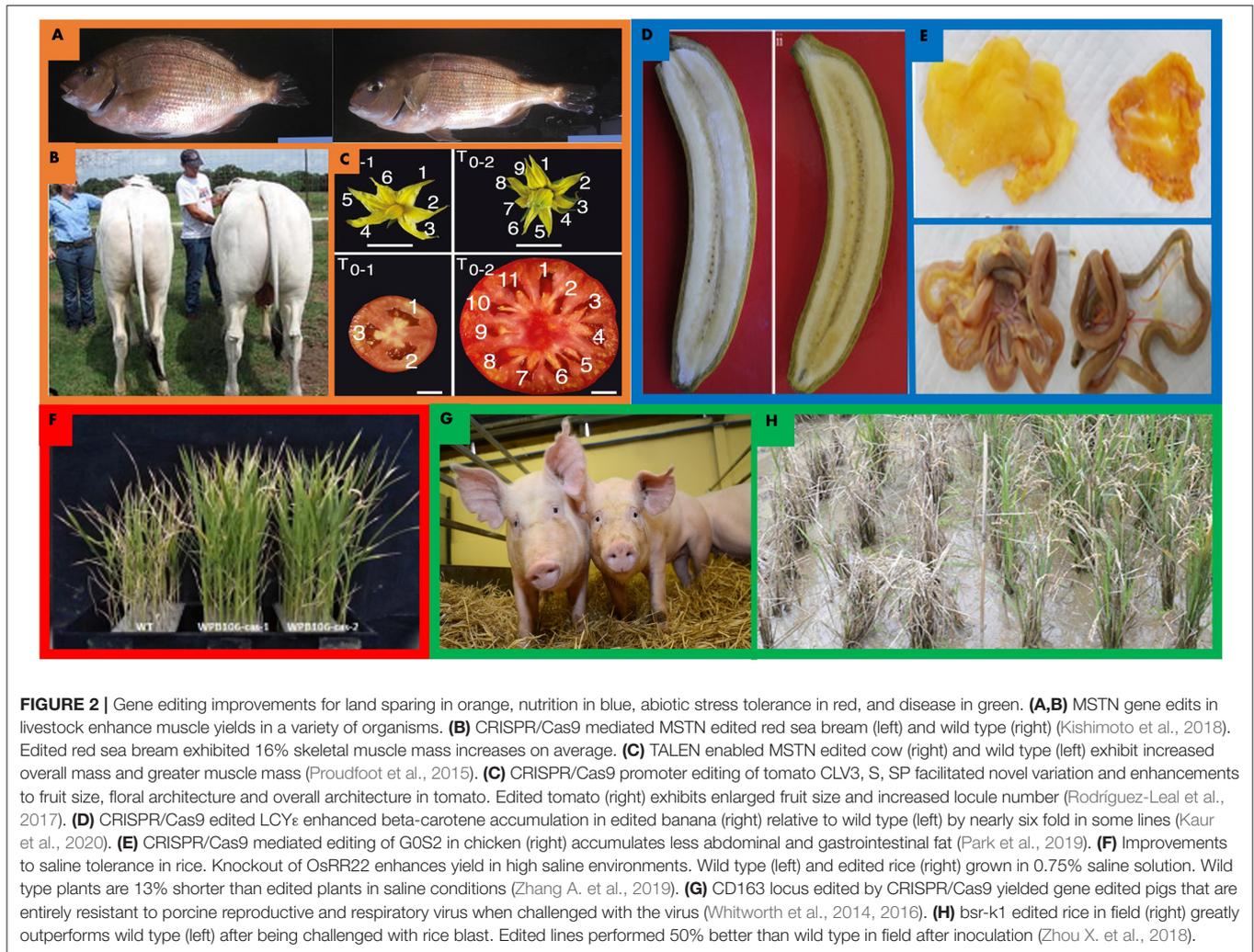
Climate change may have varying effects on diseases across geographies and temporal scales, as was indicated by modeling two prevalent rice diseases in Tanzania: leaf blast and bacterial leaf blight (Duku et al., 2016). It should be noted that these diseases are two of the most devastating rice diseases globally. The model indicated that bacterial leaf blight caused by *Xanthomonas oryzae* pv. *oryzae* (PthXo2) will likely become more severe due to climate change in Tanzania, whereas rice infection by leaf blast caused by *Magnaporthe oryzae* will decrease due to changing climate. Modeling two diseases in the same geography revealed that climate change will not always result in increased disease severity, thereby necessitating careful considerations of diseases that will indeed become worse due to climate change.

Gene editing for a range of rice diseases has proven remarkably effective. CRISPR/Cas9 was used to produce knockouts of OsSWEET13. SWEET family genes encode sucrose transporters that can be exploited by pathogens (Jiang et al., 2013). Mutating this gene increased disease resistance dramatically (Zhou et al., 2015). A similar approach to address bacterial leaf blight used CRISPR/Cas9 to target the promoter region of multiple OsSWEET genes in two studies (Oliva et al.,

2019; Xu et al., 2019). Lines that had been edited were broadly resistant to many *Xanthomonas* pathogens. The knockout of an alternative gene, Os8N3, similarly resulted in plants that were also resistant to this pathogen. Os8N3 was selected as a target based on naturally occurring resistance alleles in this gene despite the mechanisms of resistance not being well-defined (Kim et al., 2019). In the case of leaf blight, gene editing effectively reduced rice susceptibility to a pathogen that is anticipated to become more damaging in some regions of the world due to climate change.

CRISPR/Cas9 mediated knockout of OsERF922, an ethylene response gene previously implicated in blast resistance, had significantly reduced lesion sizes in response to being infected with leaf blast with no concomitant alterations to agronomic traits (Wang et al., 2016).

Editing a eukaryotic elongation factor, eIF4G, in rice, using CRISPR/Cas9 yielded plants entirely resistant to rice tungro virus. Edited plants infected with virus had no detectable viral proteins and exhibited higher yields relative to wild type (Macovei et al., 2018). Additional efforts to engineer broad-scale resistance to multiple rice pathogens simultaneously are described below.



**FIGURE 2 |** Gene editing improvements for land sparing in orange, nutrition in blue, abiotic stress tolerance in red, and disease in green. **(A,B)** MSTN gene edits in livestock enhance muscle yields in a variety of organisms. **(B)** CRISPR/Cas9 mediated MSTN edited red sea bream (left) and wild type (right) (Kishimoto et al., 2018). Edited red sea bream exhibited 16% skeletal muscle mass increases on average. **(C)** TALEN enabled MSTN edited cow (right) and wild type (left) exhibit increased overall mass and greater muscle mass (Proudfoot et al., 2015). **(C)** CRISPR/Cas9 promoter editing of tomato CLV3, S, SP facilitated novel variation and enhancements to fruit size, floral architecture and overall architecture in tomato. Edited tomato (right) exhibits enlarged fruit size and increased locule number (Rodríguez-Leal et al., 2017). **(D)** CRISPR/Cas9 edited LCYE enhanced beta-carotene accumulation in edited banana (right) relative to wild type (left) by nearly six fold in some lines (Kaur et al., 2020). **(E)** CRISPR/Cas9 mediated editing of G0S2 in chicken (right) accumulates less abdominal and gastrointestinal fat (Park et al., 2019). **(F)** Improvements to saline tolerance in rice. Knockout of OsRR22 enhances yield in high saline environments. Wild type (left) and edited rice (right) grown in 0.75% saline solution. Wild type plants are 13% shorter than edited plants in saline conditions (Zhang A. et al., 2019). **(G)** CD163 locus edited by CRISPR/Cas9 yielded gene edited pigs that are entirely resistant to porcine reproductive and respiratory virus when challenged with the virus (Whitworth et al., 2014, 2016). **(H)** bsr-k1 edited rice in field (right) greatly outperforms wild type (left) after being challenged with rice blast. Edited lines performed 50% better than wild type in field after inoculation (Zhou X. et al., 2018).

## Engineering Broad-Scale Resistance in Rice, Barley, and Tomato

Some crops have been edited to establish resistance to numerous diseases simultaneously. Engineering broad-scale resistance to disease in staple crops could provide a single approach to addressing many simultaneously worsening diseases (Xu et al., 2019). An example of this approach is the editing of *bsr-k1*, a rice gene identified to be important in disease resistance. *Bsr-k1* binds to defense related genes and promotes their turnover (Zhou X. et al., 2018). Editing this gene using CRISPR/Cas9 yielded rice plants that were simultaneously resistant to leaf blast and bacterial leaf blight by stabilizing important defense genes. Field trials of edited lines yielded 50% greater when challenged with rice leaf blast in the field. Other agronomic properties of the edited rice plants were not affected (Zhou X. et al., 2018).

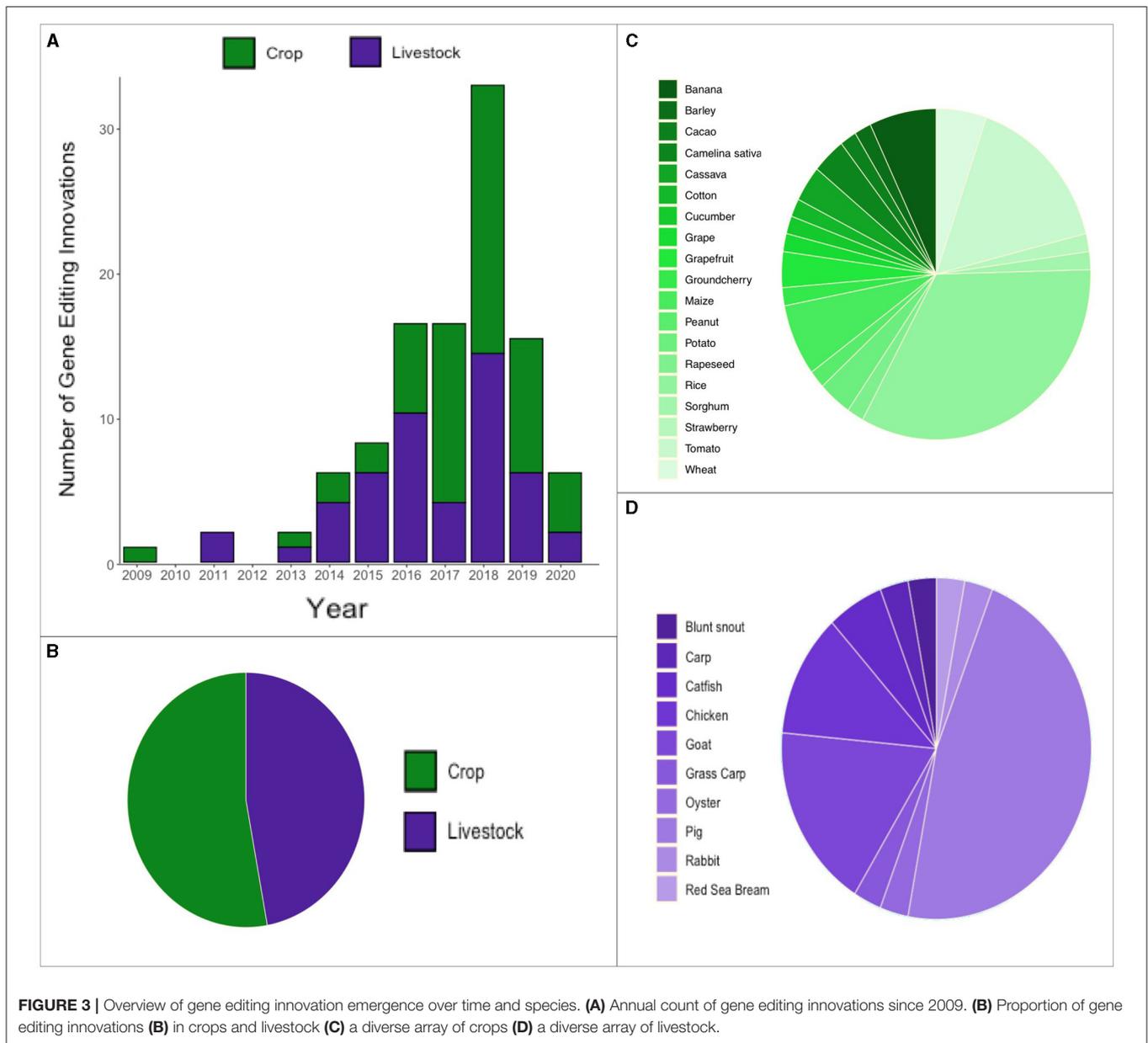
In barley, CRISPR/Cas9-mediated editing of *MORC1*, a defense related gene previously identified in *Arabidopsis thaliana*, simultaneously increased resistance to *Blumeria graminis* f. sp. *Hordei* the causative agent of barley powdery mildew and *Fusarium graminearum*. Edited

barley plants contained less fungal DNA and exhibited fewer lesions (Kumar et al., 2018).

Likewise, editing of a single locus in tomato conferred broad-spectrum resistance. Mutations to *SIDMR6-1*. Loss of function mutants in *Arabidopsis thaliana* maintain higher levels of salicylic acid. CRISPR/Cas9 edited tomato lines were more resistant to *P. syringae*, *P. capsici*, and *Xanthomonas spp.*, indicated by markedly less severe disease symptoms and lowered pathogen presence (de Toledo Thomazella et al., 2016).

## Managing Cassava Brown Streak Virus

In cassava, gene editing was used to address brown streak virus which can cause yield reductions of 70% in severe cases. Similar to host eukaryotic translation initiation factors in rice (eIF), eIF4E isoforms encoded by the cassava genome are required by Potyviridae viruses for infection. Simultaneous targeting of *ncbp1* and *ncbp2*, two such eIF4E genes, by CRISPR/Cas9 enhanced plant resistance: root disease severity and viral titer were lowered significantly in edited cassava lines (Gomez et al., 2019).



### Engineering Cucumber Viral Resistance

Likewise in cucumber, CRISPR/Cas9 was used to generate deletions in the eIF4e gene to inhibit viral infections. Lines with homozygous mutations were resistant to cucumber vein yellowing virus, zucchini yellow mosaic virus, and papaya ringspot virus-W as demonstrated by reduced symptoms and viral accumulation (Chandrasekaran et al., 2016).

### Wheat Powdery Mildew Mitigation

Wheat powdery mildew is also anticipated to become increasingly severe on winter wheat in China with the changing climate (Tang X. et al., 2017). In anticipation of this increased disease pressure, researchers in China have undertaken a gene editing effort to address wheat

susceptibility to this disease. Employing TALENs and CRISPR/Cas9, researchers successfully edited the mildew resistance locus (MLO) in the wheat genome (Wang et al., 2014). As a result, the percentage of viable powdery mildew-causing pathogens was effectively 0% in edited lines and nearly 20% in wild type. Edited plants exhibited marked improvements in powdery mildew resistance relative to wild type.

An additional effort targeting EDR1, as an alternate mechanism for achieving powdery mildew resistance was undertaken using CRISPR/Cas9: edited wheat plants like the MLO edited lines were resistant to powdery mildew indicated by reductions in fungal structures and microcolonies (Zhang et al., 2017).

## Powdery Mildew Mitigation in Tomato and Grape

Gene editing for disease resistance in non-grain crops has also been a successful endeavor. For example, in tomato, the MLO locus was also edited using CRISPR/Cas9, leading to the development of elite tomato varieties that are resistant to the powdery mildew disease as indicated by heightened hydrogen peroxide accumulation after infection with powdery mildew (Nekrasov et al., 2017). Targeting of MLO homologs in grapevine similarly increased powdery mildew resistance; in grapevine there was about a 2-fold reduction in powdery mildew sporulation in an edited line (Wan et al., 2020). It is noteworthy that homologous loci in alternate crop species gave rise to powdery mildew resistance when edited, providing an example of transferable applications of gene editing among distantly related species.

## Enhancing Resistance of Tomato to Alternate Diseases

Also in tomato, gene editing approaches have improved resistance to bacterial speck and tomato yellow leaf curl virus (Tashkandi et al., 2018; Ortigosa et al., 2019). Editing of JAZ2 in tomato using CRISPR/Cas9 reduced infection by *Pseudomonas syringae* pv. tomato, the causal agent of bacterial speck, by reducing pathogen mediated stomatal opening. Edited plants maintained significantly reduced levels of *Pseudomonas syringae* pv. tomato relative to wild type. CRISPR/Cas9 mediated resistance in tomato has also been effectively applied to manage yellow leaf curl virus. Tomato plants were engineered to contain guides targeting multiple sequences in the TYCV genome. Viral accumulation was markedly decreased in engineered tomatoes and this resistance was heritable over many generations.

## Securing Banana Resistance to BSV

In bananas, banana streak virus (BSV) presents a major barrier to breeding and distribution of banana cultivars (*Musa spp.*) in various parts of the world (Tripathi J. N. et al., 2019). This virus integrates into the B subgenome of *Musa* species and remains latent until plants encounter stress such as drought. Many important agronomic species of banana such as plantains are affected by this virus, and breeding programs are restricted in their ability to use *Musa balbisiana* as source material due to the presence of the latent virus. Knockouts of the endogenous virus produced lines in which 75% of edited plants remained asymptomatic after being exposed to water stress. This is the first study to show the efficacy of targeting an integrated plant virus in a plant genome and provides a promising mechanism to address a significant barrier in banana production and breeding (Tripathi J. N. et al., 2019).

## Transient Resistance in Cacao

In cacao, knockout-based improvement of resistance to *Phytophthora tropicalis* was achieved in a transient assay. Cacao plants transiently expressing CRISPR/Cas9 targeting the TcNPR3 gene, a suppressor of disease response, exhibited smaller lesions after infection with *Phytophthora tropicalis*. This work represents the first application of gene editing in cacao, and

paves the way for future stably heritable edited lines of cacao (Fister et al., 2018).

## Grapefruit Resistance to Citrus Canker

Citrus canker is a devastating disease in most citrus fruits especially as most commercial varieties remain susceptible to infection. Application of CRISPR/Cas9 to grapefruit has successfully increased resistance of edited fruit to infection. The causative agent of citrus canker, *Xanthomonas citri* subsp. *citri* (Xcc), is able to increase expression of CsLOB1 thus generating cankers (Jia et al., 2016). CRISPR/Cas9 mediated editing of CsLOB1 promoter binding sites (Jia et al., 2016) and the CsLOB1 coding region (Jia et al., 2017) were both effective in generating resistant grapefruit lines indicated by tremendously reduced symptoms.

## Increased Virus and Abiotic Stress Resistance in Potato

CRISPR/Cas9 mediated editing of a gene encoding coilin in potato plants has facilitated increased resistance to potato virus Y. Coilin is a major structural component of the subnuclear Cajal bodies previously implicated in virus interactions *in planta*. Modification of the potato coilin gene C-terminal domain significantly increased resistance of potato to Potato virus Y and also increased salt and drought tolerance (Makhotenko et al., 2019).

## Curing Cotton Cancer

Cotton verticillium or “cotton cancer” is a severe disease of cotton caused by *Verticillium dahliae* (Zhang Z. et al., 2018) with little resistant germplasm available in natural populations. 14-3-3 proteins c and d had been previously identified as negative regulators of disease response. Knockouts of 14-3-3 c and 14-3-3 d simultaneously yielded cotton plants that were more resistant to cotton verticillium indicated by fewer disease symptoms and lowered pathogen presence.

## Animal Gene Editing for Disease Resistance

Diseases affecting animal hosts are projected to be affected by climate change as well. The intersection of multiple climate and human variables makes it difficult to determine how climate change will affect animal pathogens (Samy and Peterson, 2016; Bett et al., 2017). It is likely that currently temperate locations will become more favorable to tropical vector-borne diseases, exposing new host populations with no previous immunity and potentially creating new disease transmission modes and patterns (De et al., 2008). Overall, there is high confidence that diseases and disease vectors will worsen due to climate change (Shukla et al., in press).

Gene editing has been used to target several animal diseases; several such studies are described below to demonstrate the state of the field. These examples are meant to demonstrate a substantial basis for the capacity of gene editing to ameliorate diseases that may potentially worsen due to climate change. The vast majority of editing for animal disease resistance centers on the creation of disease-resistant livestock, with the exception of

CRISPR-based gene drives in mosquitoes and other vector and reservoir species (Esvelt et al., 2014; Hammond et al., 2016; Esvelt and Gemmell, 2017; Champer et al., 2018; Scudellari, 2019).

### Viral Resistance in Chicken

In chickens, avian leukosis viral subgroup J is a disease that can infect meat and laying chickens, resulting in relatively high mortality rates. Researchers used CRISPR/Cas9 and homologous recombination to create an amino acid deletion in the extracellular portion of the gene *chNHE1* (chicken Na<sup>+</sup>/H<sup>+</sup> exchanger type 1), which encodes the virus receptor in chickens that allows the virus to infect cells. The deletion was completed in chicken primordial germ cells, which through transplantation and subsequent breeding resulted in chickens resistant to infection by the virus (Koslov et al., 2020).

### Tuberculosis and Mastitis Resistance in Cattle

Tuberculosis resistance in cattle has been addressed in two studies. In the first study, researchers focused on the mouse gene *SP110* (SP110 Nuclear Body Protein), which controls *Mycobacterium tuberculosis* (MTB) infections and induces apoptosis in infected cells (Wu et al., 2015). The authors used TALEN Nickases to insert the gene into a specific location in the bovine genome via homologous recombination; the knock-in of this resistance gene improved tuberculosis resistance (Wu et al., 2015). A second study using CRISPR/Cas9 was able to knock-in the *NRAMP1* gene (natural resistance-associated macrophage protein-1, a gene associated with innate immunity) from bovine via homologous recombination. The resulting cattle likewise exhibited increased tuberculosis resistance (Gao et al., 2017).

Similarly, gene editing has been utilized to prevent mastitis, the most significant disease of dairy cows. In two studies, homologous recombination in cattle facilitated by ZFN Nickases enabled the insertion of two genes that confer resistance to infection from *S. aureus*, a causative agent of mastitis: the gene encoding lysostaphin from *Staphylococcus simulans* (Liu et al., 2013) and the human lysozyme (hLYZ) gene (Liu et al., 2014) into an intron of the  $\beta$ -casein locus of dairy cattle. Because casein is a protein found in dairy milk, the genes inserted into this locus would mimic expression of  $\beta$ -casein and the exogenous proteins would be present in milk produced from the edited cows (Liu et al., 2013). Both of these studies yielded dairy cows with milk that was able to prevent *S. aureus* infection of the lactating cow.

*M. haemolytica* is a causative agent of pneumonia in cattle. ZFNs were used to make a precise edit in *CD18*, a gene encoding a surface protein on cattle leukocytes. Leukocytes extracted from the edited cow exhibited very low levels of cell toxicity in the presence of *M. haemolytica* leukotoxin relative to wild type cattle. Thus, a gene edit markedly improved the tolerance of gene edited cattle to *M. haemolytica*, a pervasive agent of disease (Shanthalingam et al., 2016).

### Disease Resistance in Pigs

Progress has also been made in developing disease resistance in pigs using gene editing. In a 2014 study, researchers were able to knock out two genes, *CD163* and *CD1D* (Whitworth et al., 2014). The former is required for infection by porcine

reproductive and respiratory syndrome virus (PRRS virus), and the latter is involved in innate immunity. In a follow-up to this study, the researchers assessed the *Cd163* knockout pigs for resistance to PRRS, finding that they displayed no symptoms when infected. In comparison, wild-type offspring developed severe symptoms necessitating their euthanization (Whitworth et al., 2016). Similar results were also obtained by a later study, also using CRISPR/Cas9 editing to knock out *CD163* to produce pigs fully resistant to PRRSV (Burkard et al., 2017, 2018).

Further work in pigs was able to demonstrate the utility of CRISPR/Cas9 to knock-in resistance to classical swine fever virus (CSFV) at the *Rosa26* locus (Xie et al., 2018). This locus is a preferred site for transgene insertion due to its ubiquitous and strong expression, coupled with a lack of gene-silencing effects (Irion et al., 2007; Xie et al., 2018). The edited pigs were resistant to CSFV, whereas all wild type pigs exhibited 100% mortality. Researchers were also able to knock-in the *C. elegans fat-1* gene into the *Rosa26* locus in pigs (Li M. et al., 2018). As *fat-1* is implicated in both disease resistance and nutritive quality of meat, this study served as a proof-of-concept to demonstrate the possibility of simultaneously improving the nutritional value of pork and increasing general disease resistance in pigs. Finally, a recent study was able to use CRISPR/Cas9 editing to knock out the *ANPEP* (aminopeptidase N) gene, conferring resistance to infections caused by coronaviruses (Whitworth et al., 2019).

### Viral Resistance in Aquatic Species

Use of gene editing to combat disease in aquatic species is more limited; the first use of a CRISPR system to test enhanced disease resistance was in 2018 (Ma et al., 2018). Here, researchers were able to use CRISPR/Cas9 in grass carp cell lines to knock out *gcJAM-A* (grass carp Junctional Adhesion Molecule-A), a gene involved in grass carp reovirus (GCRV) infection. When challenged with GCRV, the edited cells were shown to suppress viral replication (Ma et al., 2018).

In crops and livestock, genes have been identified that increase disease resistance when knocked out. Altering genetic elements involved in susceptibility has thus far been the primary form of disease mitigation through gene editing for crops. Whereas, in livestock, gene editing has facilitated the knockout and knock-in of genes to improve disease resistance. Successful gene editing studies in crops and animals provide a reasonable foundation for further use of this technology to address a range of diseases, some of which may be exacerbated by climate change.

## INCREASING YIELDS

Global climate change will continue to broadly reduce crop and livestock yields (Lobell and Gourdji, 2012). Some landscapes will experience yield improvements, but largely climate change stands to lower productivity (Shukla et al., in press). Coupled with population increases, these coinciding phenomena will necessitate the expansion of agricultural lands into currently non-cultivated geographical areas. This expansion imposes a severe threat to biodiversity and the associated ecological services of non-agricultural lands. Land sparing through the augmentation of yield can mitigate the deleterious effects of agricultural

expansion, with gene editing as a potential tool toward this solution (Table 3, Figure 2).

## Crop Yield Improvement

### Improving Rice Yields

In crop plants, a variety of gene edits have been produced to increase yields. In rice, for example, targeting different combinations of genes associated with yield restrictions has produced lines with 11–68% increased yields (Huang et al., 2018; Miao et al., 2018; Zhou et al., 2019). *DEP1* and *Gn1a* are yield-associated genes that have been previously characterized for their involvement in yield attributes. One novel allele of *Gn1A* and three novel alleles of *DEP1* generated by CRISPR/Cas9 produced significantly higher yields relative to wild type alleles. *Gn1A* novel mutants yielded >24% which was slightly better than the 21% yield advantage conferred by natural mutant *Gn1A*. Novel mutants in *DEP1* yielded up to 51% greater than WT which is 11% greater than the naturally occurring mutants (Huang et al., 2018).

In another case simultaneous and individual knockouts of three yielded related genes, *GS3*, *GW2*, and *Gn1a*, identified to negatively regulate grain size, width, and number, respectively, increased yield in rice in three different cultivars. Simultaneous KOs generated greatest yield increases, with gains of up to 68% in one cultivar. Multiple knockouts can thus be additive in yield improvements (Zhou et al., 2019).

CRISPR-Cas9 induced mutations in class I *PYL* genes were also able to increase yield. Abscisic acid (ABA) is a *PYL/RCARs* are genes that encode receptors for ABA, a phytohormone essential in drought responses and in seed dormancy. Simultaneous mutations of class I *PYL* genes resulted in rice plants that were higher yielding in paddy conditions. The stomata in *PYL* mutants were much less responsive to the addition of ABA, maintaining larger apertures despite the presence of the drought signal. Thus, the mutant plants lost water more readily. The resultant plants had larger panicles, greater panicle branches, more tillers, and overall higher yield when tested in field conditions. This approach could be appropriate for rice grown in paddy conditions but would be deleterious in conditions where water is limited. Triple knockout of *PYLs* 1,4,6 afforded a 30% increase in yield in well-watered conditions (Miao et al., 2018).

### Knockout-Based Wheat Yield Improvement

In wheat, simultaneous knockouts of *GW2*, *LPX-1*, and *MLO* were meant to enhance yield and disease resistance. Genes selected were previously shown in separate studies to increase yield and wheat pathogen resistance. Homozygous, simultaneous mutations in these three loci yielded wheat plants that had significantly elevated grain weights and size, while disease resistance was not evaluated (Wang et al., 2018).

### Improving Yields of Waxy Maize

In maize, CRISPR/Cas9 was used to generate high amylopectin varieties from elite cultivars by knocking out the waxy gene. Gene edited varieties yielded 5.5 bushels more per acre relative to high amylopectin varieties generated by conventional breeding

and were produced in less time, highlighting the throughput and utility of gene editing relative to conventional breeding in certain specific applications (Gao et al., 2020).

## Engineering Tomato Architecture and Domestication for Yield

Engineering of tomato architecture using CRISPR/Cas9 has enabled improvements such as drastically increased fruit size and altered plant morphology better suited for urban environments (Rodríguez-Leal et al., 2017; Lemmon et al., 2018). Promoter editing of *SlCLV3*, a mobile peptide important in floral stem cell regulation, *S*, and inflorescence architecture gene, and *SP*, an overall architecture gene, were able to generate novel variation and enhancement in fruit size, floral architecture and overall architecture in tomato. This study also provided major breakthroughs in the use of gene editing cis-regulatory elements for crop improvements.

Efforts have been made to increase yield as well as other agronomic properties of tomatoes using CRISPR/Cas9 to domesticate a wild tomato variety. By identifying and editing six genes associated with key domestication traits, researchers were able to domesticate a wild tomato relative, increasing fruit size 3-fold and fruit number 10-fold. and yield while also improving nutrition, abiotic stress tolerance, and disease tolerance. This study also provides the basis for future gene editing mediated wild relative domestications (Zsögön et al., 2018).

## Livestock Yield Improvement

### Enhancing Livestock Yield Through *MSTN* Knockouts

In animal gene editing, many efforts have converged on targeting the *MSTN* gene in species such as pig, cattle, sheep, goat, rabbit, and several aquatic animals including carp, catfish, and red sea bream (Dong et al., 2011; Han et al., 2014; Luo et al., 2014; Ni et al., 2014; Crispo et al., 2015; Proudfoot et al., 2015; Qian et al., 2015; Wang K. et al., 2015; Wang X. et al., 2015; Bi et al., 2016; Guo et al., 2016; Li et al., 2016; Rao et al., 2016; Tanihara et al., 2016; Yu et al., 2016, 2019; Zhong et al., 2016; Khalil et al., 2017; Wang et al., 2017; He et al., 2018; Kishimoto et al., 2018; Su et al., 2018a; Zhang J. et al., 2018; Zhang Y. et al., 2019; Sun et al., 2020). The *MSTN* gene (also known as *GDF8*) encodes the gene for myostatin, a growth differentiation factor that inhibits muscle growth. In natural cattle populations *MSTN* mutations underlie the double-musled phenotype (McPherron and Lee, 1997). Successful *MSTN* knockout animals exhibit significantly higher muscle mass than those with the functional *MSTN* gene. Assessment of *MSTN* knockouts tend to vary, with some studies comparing birth weight, body weight-to-muscle mass, muscle fiber number, muscle weight, and muscle size between edited and unedited animals. Combined with several bottlenecks in efficiency of editing, comparing the outcomes of each study to another can be challenging. ZFN, TALENs, and CRISPR/Cas9 have all been utilized to achieve *MSTN*-edited animals.

Studies that assessed the phenotypes of edited *MSTN* pigs reported increased birth weight (Wang K. et al., 2015), body weight-to-muscle mass ratio equaling 170% that of unedited pigs (Rao et al., 2016), and upwards of 100% increased muscle mass (Qian et al., 2015). Other studies reported an obvious

double-muscled phenotype (Tanihara et al., 2016; Wang et al., 2017), or significantly larger muscles (Bi et al., 2016), but not all studies reported an assessment of the edited pig phenotype (Su et al., 2018a). Comparatively fewer studies on *MSTN* knockouts have been conducted in cattle, although two performed in 2014 resulted in edited animals with an obvious double-muscled phenotype (Luo et al., 2014; Proudfoot et al., 2015).

Faster growth (Crispo et al., 2015) and increased body weight of up to 60% (Li et al., 2016) were found in sheep, with similar results in goats (Ni et al., 2014; Yu et al., 2016; He et al., 2018). Studies performed as early as 2014 reported successful editing in sheep (Proudfoot et al., 2015), but phenotypic assessment in all cases is still lacking (Han et al., 2014), or limited to microscopy of muscle tissue (Zhang Y. et al., 2019). One study edited both goats and rabbits; while both exhibited increased weight ratios of biceps and quadriceps upwards of 50%, the rabbits tended to have very large tongues and low viability (Guo et al., 2016). Other studies in goats successfully targeted another gene, *FGF5*, in addition to *MSTN* (Wang X. et al., 2015), or inserted an additional gene, *fat-1*, into the *MSTN* locus (Zhang J. et al., 2018).

*MSTN* has also been targeted in several aquatic species, with the first heritable *MSTN* knockout in an aquaculture species being performed by ZFN in 2011 (Dong et al., 2011). TALENs and CRISPR/Cas9 were later used to edit carp, a tetraploid species, although severe bone defects were present in addition to enhanced muscle mass (Zhong et al., 2016). Successful editing followed in several aquaculture species such as catfish, which resulted in a 29.7% increase in catfish fry body weight (Khalil et al., 2017), red sea bream, which resulted in a 16% increase in muscle mass (Kishimoto et al., 2018), and blunt snout bream, which resulted in a 7% increase in body weight (Sun et al., 2020). Outside of fish there has also been one successful *MSTN* knockout in pacific oyster, a major aquaculture bivalve (Yu et al., 2019).

While *MSTN* editing appears quite promising for improving animal yields, the drawbacks of this gene target must also be considered. For example, increased birth weight of edited animals can result in birthing challenges, and viability has been an issue in several studies (Wang X. et al., 2015; Rao et al., 2016). Fine-tuning *MSTN* mutations beyond complete knockouts could serve to optimize the use of this gene as a land sparing tool. Additional targets for increasing biomass beyond *MSTN* should also be considered. For instance, of *MSTN* mutations, other studies in pigs have targeted knockouts for increased muscle mass (Xiang et al., 2018; Zou Y. et al., 2018; Liu et al., 2019).

### Enhancing Livestock Yields Through Alteration of Sex Ratios

Livestock gene editing has also been employed to alter sex ratios of offspring. In many production schemes, only a single sex is required (i.e., female chickens in laying operations). Increasing ratios of the preferred sex in offspring stands to lower inputs and space typically allocated to rearing animals which are unfit for the desired production. An effort in chicken editing used CRISPR/Cas9 to insert a fluorescent protein into the male sex chromosomes thus facilitating high-throughput sex determination during embryogenesis (Lee et al., 2019). A system

to produce exclusively female offspring in mice by targeting exclusively male genes has been developed with potential for transferral to alternate mammalian species (Yosef et al., 2019). Ongoing works seeks to improve sex-determining and sex-biasing technologies to facilitate land and resource sparing in livestock operations (Kurtz and Petersen, 2019; Douglas, 2020; CSIRO, 2021), and avenues for increasing litter size in general are being explored: one study succeeded in mutating the *GDF9* gene to increase litter size in goats (Niu et al., 2018).

Land sparing is not the only method by which the ecological consequences of agriculture can be buffered; one alternative is land sharing (Phalan et al., 2011; Soga et al., 2014). Most of the efforts undertaken by researchers to date are intended to be compatible with a land sparing approach however. Gene editing for increased yields of plants and animals has been considerably effective in research studies and could act to prevent the sprawl of agricultural production.

## ENHANCING NUTRITION

At the end of 2019, 690 million people worldwide were suffering from undernourishment, or the insufficient consumption of calories (Von Grebmer et al., 2020). This pandemic stands to worsen as climate change exacerbates yield deficits and pest pressure. Much more pervasive however is malnutrition, which encompasses undernourishment as well as micronutrient deficiencies and overconsumption of calories. As of 2014, ~2 billion individuals suffered from micronutrient deficiencies (Von Grebmer et al., 2014).

Climate change is currently contributing to malnourishment in several ways and is predicted to worsen. More extreme climatic conditions will disrupt food chains and increase food prices, with tropical and subtropical regions experiencing the worst effects of crop yield decline (Shukla et al., in press). Prolonged droughts, which are projected to increase, reduce root acquisition of water soluble nutrients such as nitrate, sulfate, calcium, magnesium, and silicon. Additionally as erratic rainfall episodes worsen, more nitrate is expected to leach from soils (St.Clair and Lynch, 2010).

The increased level of CO<sub>2</sub> will also be detrimental to nutritional quality of many crops (Soares et al., 2019; Shukla et al., in press). Wheat grown at projected mid-to-late 21st century CO<sub>2</sub> levels has been found to have reduced protein, zinc, and iron (Shukla et al., in press), and similar nutrient decreases have been observed in rice, legumes, and several vegetables (Soares et al., 2019). A modeling study predicted that climate change has placed many fruits and vegetable crops at a high risk of going extinct (Springmann et al., 2016). In addition, lack of reduced intake of fruits and vegetables caused by limited access could double the number of deaths caused by malnutrition by 2050 (Springmann et al., 2016). Projections indicate that at the current rate of CO<sub>2</sub> emissions, an additional 1.9% of the global population will become deficient in zinc, 1.3% will be protein deficient, and 57% of children and childbearing-aged women will live in geographies at high-risk of iron deficiencies, by 2050 (Smith and Myers, 2018).

Gene editing may play a role in ameliorating the current and future states of the malnourishment pandemic beyond

providing increased yields. Recent work applied to plants and livestock has indicated that gene editing may effectively increase desirable nutritional metabolites, reduce anti-nutrients, and alter macronutrients in ways that can be advantageous for human health (Table 4, Figure 2).

### Increasing Beneficial Metabolites

The color pigments of crop plants such as anthocyanins, lycopene, carotenoids are known for possessing high antioxidant vitamins, necessary for improving nutrition and fighting disease. Anthocyanins help in reducing inflammation and preventing oxidative damage to cells while beta-carotene (a precursor to vitamin A) is essential for vision and other immune functions (Tanaka and Ohmiya, 2008). In rice, CRISPR/Cas9 editing facilitated the insertion of carotenoid biosynthesis genes in a precise genomic location to increase carotenoid accumulation (Tanaka and Ohmiya, 2008) that could further advance earlier efforts to engineer “Golden Rice.” These fortified lines stand to benefit the poorest women and children in developing countries with rice-dominant diets, such as Bangladesh. Likewise, proanthocyanidins, and anthocyanins augmentation has been pursued in rice (Zafar et al., 2020) and other species. In tomato, CRISPR/Cas9 editing has been used to target a series of genes, resulting in yellow, pink and purple colored tomatoes respectively (Cermák et al., 2015; Filler Hayut et al., 2017; Deng et al., 2018). The insertion of a strong promoter via CRISPR/Cas9 upstream of *ANT1*, which codes for a Myb transcription factor, resulted in anthocyanin accumulation manifested by an intense purple color in tomatoes (Cermák et al., 2015). The Phytoene synthase gene (*Psy1*) and other carotenoid biosynthesis genes have also been targets of genome editing that significantly increase lycopene content in tomatoes (Li X. et al., 2018). In addition, domestication of a wild tomato using gene editing produced tomatoes with 500% increased accumulation of lycopene (Zsögön et al., 2018). Dramatic enhancements of beta-carotene in banana fruit were facilitated by a CRISPR/Cas9 mediated knockout (Kaur et al., 2020). This color variation holds a great potential for improving consumers’ appeal for variety, while broadening intake of healthy pigments.

Gene editing approaches have been most commonly applied to commodity crops. However, great potential of these tools lies in improving nutrition of non-staple, regionally relevant fruits and vegetables. For example, the tools of gene editing are being applied to further domesticate and improve new “super foods” from tomato’s lesser known relatives in the *Physalis* genus such as goldenberry and groundcherry (Lemmon et al., 2018). Many of these species are rich in minerals, macro- and micronutrients and bioactive compounds such as antioxidants, vitamins A, B, and C, and have been long-used as folk remedies for diseases still relevant today (Shenstone et al., 2020). Early results suggest that CRISPR/Cas9-mediated deletions of previously identified agronomic genes may improve the cultivability of nutritional berries such as the ground cherry (Lemmon et al., 2018), rendering it more economically viable for commercial production.

The Fatty Acid Desaturase 2 (*FAD2*) gene determines the levels of monounsaturated fats in most oil producing crops;

gene editing tools have been used to induce mutations in this gene, leading to a significant change in their level. In the emerging oil seed crop, *Camelina sativa*, targeted CRISPR/Cas9 editing, increased total seed oleic oil composition by more than 50% in some cases while reducing linoleic and linolenic acid levels (Jiang et al., 2017; Morineau et al., 2017). Similarly, oleic acid content has been improved in *Brassica napus* (Okuzaki et al., 2018). Shifts in seed oil composition are thought to be advantageous nutritionally and to extend shelf-life of oil extracts (Jiang et al., 2017; Morineau et al., 2017). Applications of TALEN-mediated editing to soybean facilitated the development of a high oleic and low linolenic acid soybeans (HOLL). Oil extracted from these modified soybeans could bypass the need for hydrogenation, a process which generates unhealthy trans-fats (Demorest et al., 2016). HOLL soybeans are being developed for commercialization by Calyxt Inc. with hopes of release by 2022 (Calyxt, 2019).

Similar efforts are underway using TALEN-mediated mutagenesis of *FAD2* gene to increase oleic acid content of peanut (Wen et al., 2018).

### Modifying Macronutrients

In addition to augmenting levels of beneficial metabolites, gene editing has made improvements to macronutrients possible. In rice, knockouts of the *SBEIIb* gene associated with amylopectin biosynthesis decreased levels of amylopectin in favor of amylose in the grain endosperm (Sun et al., 2017). Conversely, other food crops such as cassava have been targeted for reduced starch content through editing two genes involved in amylose biosynthesis (Bull et al., 2018). A knockout of the *GBSS* gene in potato using CRISPR-Cas9 also led to an altered starch content (Andersson et al., 2017). In strawberry, gene editing has been used to develop a continuum of altered sugar content (Xing et al., 2020). As demonstrated, gene editing can be used to fundamentally alter the composition of macronutrients for nutritional improvements.

### Lowering Anti-nutritional Compounds

Gene editing has also been applied to numerous plant species to limit the accumulation of anti-nutritional components such as phytic acid in maize, which is disruptive to the nutrition of monogastric animals (Shukla et al., 2009; Liang et al., 2014). To mitigate the deleterious effects of phytic acid on iron, zinc and calcium absorption, CRISPR/Cas9 and ZFNs were used in separate studies to mutagenize genes in the phytic acid pathway, indicating the potential utility of gene editing for anti-nutritional mitigation (Liang et al., 2014). In sorghum, an important food crop in drought-prone areas, a major class of storage proteins called kafirins leads to a poor protein digestibility. By targeting genes that synthesize kafirins, researchers have successfully reduced kafirin levels and improved protein quality and digestibility (Li et al., 2018). In a similar effort, Tang et al. engineered a rice variety to prevent the accumulation of cadmium in rice grains using CRISPR/Cas9 (Tang L. et al., 2017).

In chickens, gene editing has driven improvements of nutritive properties by reducing fat. Using CRISPR/Cas9 to target

the GOS2 gene known to influence lipid catabolism yielded chickens with dramatically reduced abdominal fat deposition, with no observed side-effects (Park et al., 2019). As previously mentioned, the knockin of fat-1 in pigs enhanced the nutritional value of pork by altering accumulation of beneficial fatty acids (Li M. et al., 2018). Gene editing has also been used to reduce the allergenicity of globally important commodities such as milk and wheat (Yu et al., 2011; Su et al., 2018b; Sánchez-León et al., 2018).

In animals and crops, gene editing has been leveraged to improve the nutritional aspects of these foodstuffs. This technology has enabled micronutrient improvements, anti-nutritional component reduction, macronutrient modifications, and removal of allergens. In anticipation of the severe impacts of climate change on nutrition, gene editing could serve as a potent adaptive mechanism across a suite of commodities and nutritional traits.

## LIMITATIONS AND OPPORTUNITIES

Gene editing has already been applied successfully to plants and animals in research settings to address the effects of climate change **Tables 1–4, Figures 2, 3**. However, there are still significant limitations to its efficacy in enabling climate change mitigation and adaptation. One of the most prominent limitations of current applications is the narrow scope of potential solutions without the use of intra-, cis-, and transgenic approaches. In most of the examples described, researchers produce mutations of genes whose knockout contributes positively to a trait. However, it is more common that loss-of-function mutation detracts from the organism's performance. Thus, seeking to produce improved plants solely through loss-of-function mutation significantly limits the range of possible improvements. Intragenics, cisgenics, and transgenics have a proven record in research settings of improving plant performance in a range of environments and conditions (Klümper and Qaim, 2014; Laible et al., 2015; Steinwand and Ronald, 2020). These approaches are able to leverage a vast range of genomic sequences for use in plant and animal improvements. Gene editing in conjunction with intra-, cis-, and transgenic approaches is especially beneficial. For example, CRISPR/Cas9 was used to precisely insert a promoter present in the maize genome upstream of a gene that contributes to drought tolerance (Shi et al., 2017). This novel recombination of genetic elements native to the maize genome via CRISPR/Cas9 in an intragenic approach improved drought tolerance. However, genetic elements from sexually incompatible organisms can also provide potent mechanisms for improving performance. In cows for instance, a knock-in of a mouse resistance gene using TALENs enhanced tuberculosis resistance (Wu et al., 2015). Gene editing in conjunction with ICT approaches is especially beneficial. While significant improvements through loss-of-function gene editing and intragenic approaches are demonstrably effective, greater opportunity exists in leveraging the totality of genetic diversity. Thus, regulatory barriers to use of gene editing in conjunction with ICT approaches must be addressed to maximize the potential of agricultural improvements.

Opportunities to address climate change with gene editing continue to expand as new technologies emerge. For example, alternatives to the traditional Cas9 protein for editing are being developed. Base editors that facilitate precise nucleotide modifications, epigenome modifiers that alter DNA confirmation and associated expression levels, and prime editing for precise insertion of short DNA fragments are promising candidates in this regard (Xie et al., 2018; Roca Paixão et al., 2019; Lin et al., 2020). Additionally, new techniques are emerging to improve the rates of homologous recombination, a current major limitation in plants (Huang and Puchta, 2019).

To maximize the utility of these emerging editing tools, bottlenecks in delivery must be surmounted. For livestock, the current largest barrier to editing tends to be the production of homozygous, non-mosaic, gene edited animals. Two methods currently exist to generate edited embryos prior to their transfer to a surrogate mother: one uses somatic cell nuclear transfer (SCNT) from an edited cell line to produce an edited embryo, while the other uses direct editing of a zygote. In the former case, sequencing can quickly confirm homozygous edits prior to embryo implantation, but is burdened by the inefficiency of SCNT. In the latter case, breeders can forgo SCNT but are unable to verify homozygous edits until the animal is born (Bishop and Eenennaam, 2020).

Similarly in plant regeneration, tissue culture is limiting in its species range and efficacy. To enable a broad spectrum of solutions in this space, tissue culture resources for a broader set of species must be developed. Tools for increasing the transformability of recalcitrant varieties and species are currently underway and show great promise for gene editing-based climate change solutions (Altpeter et al., 2016; Maher et al., 2020). These emerging technologies could foster further improvements in climate change performance.

Explorations of limitations beyond technical applications are not within the scope of this review, but are germane nonetheless. Consumer acceptance, policy frameworks, and economic feasibility will all factor into the ultimate success of the applications discussed.

## Gene Editing Opportunities for African Crops and Livestock

The African continent is poised to benefit greatly from advances in gene editing research for agriculture. The Green Revolution, which bolstered the agricultural yields in Central America, South America, and Asia, largely overlooked African agriculture (Toenniessen et al., 2008). Despite significant progress made to improve food insecurity in developing nations, diseases and pests still plague most of the region's agriculture. Irregular weather patterns, insect swarms and natural disasters have also impacted agriculture in the region. Climate change will not only affect Africa severely and variably according to the diverse geographies, but Africa's susceptibility to climate change hinges on non-climate related vulnerabilities including but not limited to high prevalence of malnutrition, low literacy rates, and high population growth rates (Nkomo et al., 2006). As such, there

is much potential to focus research efforts on the crops and livestock that are dominant and specific to Africa.

### Gene Editing for Disease Resistance

African staples including African banana, plantain, cassava, and yam are actively being edited for eventual application in agricultural production. Comparable to crops like wheat, rice, maize, or potatoes in other parts of the world, these staples contribute majorly to the income of small-holder farmers in Africa. Biotic and abiotic factors including diseases and pest infestation, drought, flooding, etc affects the productivity of these crops. Using gene editing, scientists are targeting these crops to withstand these challenges.

For example, researchers are using this breeding approach to improve resistance to cassava brown streak disease (Gomez et al., 2019), a disease that significantly limits the production of the crop. In addition, attempts were made to engineer resistance to African cassava mosaic virus (ACMV). However, resistance to ACMV was not achieved in the glasshouse experiment, providing evidence of the mutagenic nature of this virus and potential for further studies (Mehta et al., 2019). In banana and plantain, a gene editing system has been applied in developing disease resistant varieties. Using Cas9, Cas12, Cas13, and Cas14 enzymes, this system enabled the detection of gene sequences that informed its potential application in plant disease diagnosis (Tripathi J. N. et al., 2019).

Furthermore, a proof of concept on the potential of using gene-editing technology for the development of novel sources of resistance to rice yellow mottle virus; maize lethal necrosis, a severe disease of maize in East Africa; and striga resistance in sorghum through a Low Germination Stimulant 1 (LGS1) gene knock-out are actively being developed by numerous researchers in Africa (Karembu, 2021).

### Gene Editing for Yield Increase and Abiotic Stress Resistance

Targeting abiotic stresses, the first successful CRISPR/Cas9-mediated gene knockout system in African sorghum varieties and cowpea have recently been reported (Che et al., 2018). Recently, gene-editing has been used to target a visual marker gene in yam enabling potential rapid improvements by bypassing yam's long breeding-cycle (Syombua et al., 2019) and to develop climate-smart banana varieties with multiple and durable resistances to extreme temperature and drought (Tripathi L. et al., 2019). In maize, researchers have used CRISPR/Cas9 to develop lines tolerant to drought, DNA damage, and oxidative stress by altering the expression of poly(ADP-ribose) polymerase (PARP), which is responsible for maintenance of the energy homeostasis during stress conditions (Njuguna et al., 2017).

Furthermore, researchers have provided an example of how gene editing could be used to target and improve the yield potential of Kabre rice, thus enhancing the domestication of African rice landraces (Lacchini et al., 2020). Similarly, a proof of concept is being developed for the application of genome editing in developing wheat varieties tolerant to drought. Through employing CRISPR-Cas9 to inactivate the *Sall* genes in wheat,

the project will determine if wheat *sall* mutant plants will show an improved tolerance to drought stress (Karembu, 2021; USDA ARS, 2021).

### Gene Editing for Nutritional Enhancement

Nutritional enhancement is another major focus of some gene editing research in Africa. Scientists have demonstrated how gene editing could be used to improve the nutritional contents and yield of cassava. Similarly, the technology is being used to reduce the level of erucic acid in Ethiopian mustard (*Brassica carinata*) varieties. While current research shows that the mustard varieties available in market are above the acceptable level of total fatty acid content, gene editing could be used to edit targeted genes for improvement of nutritional content of these mustard varieties (Karembu, 2021). In targeting both improved yield and enhanced beta carotene content in sweet potato, scientists are employing gene editing technology to knock out the genes involved in converting beta carotene into other products (Joseph, 2021).

### Gene Editing for Livestock Improvement

Ongoing work in the application of gene editing for African livestock holds promise for meeting the agricultural demands of this uniquely poised continent. Private-public partnerships between African livestock research centers, with support and funding from the Bill & Melinda Gates Foundation and other donors seek to improve African livestock. Numerous opportunities exist for editing African breeds of cows and chickens for improved stress and disease tolerance. For example, to combat animal trypanosomiasis, a proof of concept has been demonstrated to introduce the Apolipoprotein L1 (ApoL 1) gene, which has been found to confer resistance to trypanosomiasis in primates (O'Toole et al., 2017), into goats using CRISPR/Cas9 (Karembu, 2021). Additionally, researchers are accelerating the rate of development of the African Swine Fever Virus (ASFV) vaccine using CRISPR/Cas9 and synthetic biology technologies (Abkallo, 2020). Furthermore, gene editing is being used to edit virulence genes of *Theileria parva* to increase the immune response of cattle when they are vaccinated against East Coast fever (ECF) (Karembu, 2021). To confer protection against the Avian influenza virus (AIV) infection in poultry, researchers are using gene-editing tools to generate variations in ANP32A, a gene that affects AIV replication. This will enable them to predict which of these targeted changes on the ANP32A gene will make the most significant restrictive effect on avian influenza virus replication (Karembu, 2021).

While most gene editing product development is at the proof-of-concept phase, the tools present many opportunities to potentially reduce the amount of time it takes to bring improved crop and animal varieties to the market in sub-Saharan Africa. Interestingly, countries like Kenya and Nigeria have made adequate provisions in their biosafety framework to ensure that these gene edited products will not be treated differently from conventional crops (Komen et al., 2020). These favorable policies will also provide the basis for future editing with broad application in enhancing climate adaptations for African agriculture.

## CONCLUSION

Gene editing is an emerging and increasingly prominent approach in plants and animals applied in response to current, and anticipation of future, climate change. Solutions provided by gene editing have the potential to stand alone or be adopted concomitantly with other climate-smart solutions. The range of gene editing applications for climate change is summarized in **Tables 1–4**, **Figures 2, 3**. Many of these applications have converged on traits such as disease resistance, nutritional improvements, abiotic stress tolerance and yield increases, but these are by no means representative of the breadth of opportunities that exist.

The emergence and application of CRISPR/Cas9 based editing in crops and livestock has facilitated a recent increase in the application of gene editing for climate change.

Despite its success in a research context, gene editing for climate change has largely not yet transitioned to real application. Adoption of these technological innovations has been stifled by regulatory barriers, social barriers, and prohibitive policies, among other externalities beyond the technical limitations described. A majority of the advances in gene editing applications for agriculture have occurred recently, which also explains, in part, the relatively low throughput to agricultural production. The ongoing efforts of public and private institutions alike, are rapidly expanding on current technological innovations.

While it should be noted that gene editing is not the sole promising agricultural improvement mechanism, the potency of this technology in providing solutions for climate change in agriculture cannot be overlooked. Gene editing, as demonstrated by the numerous studies summarized herein, stands to provide marked enhancements in agriculture to address climate change.

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## DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

## AUTHOR CONTRIBUTIONS

NK and WH developed the concept and completed much of the research, and writing. SE and MA supported the writing and editing of numerous sections. All authors contributed to the article and approved the submitted version.

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## GLOSSARY

**Cisgenic:** an organism engineered to contain genetic material derived from a sexually compatible species.

**Climate adaptation:** the process of adjusting to an anticipated climate and its associated conditions, including but not limited to altered temperature and precipitation.

**Climate mitigation:** the process of limiting the magnitude of climate change, usually by reduction or removal of greenhouse gases.

**Homologous recombination:** exchange of genetic material between a host organism and a desired template strand of DNA that encodes for the genetic material to be inserted flanked by regions that are complementary to adjacent sites in the host genome.

**Intragenic:** an organism engineered to contain only native genetic elements in a novel configuration.

**Knock-in:** a gene-editing approach in which genetic elements of interest are precisely inserted into a pre-defined locus.

**Knockdown:** a targeted mutation that reduces the expression of a gene.

**Knockout:** a targeted mutation that yields a non-functional gene product, synonymous with loss of function.

**Promoter:** the nucleotide sequence preceding a gene that specifies that gene's expression profile.

**Transformation:** process in which DNA is inserted into the genome of an organism.

**Transgenic:** an organism engineered to contain genetic material from a sexually incompatible organism.

**Wild type:** the typical form of a gene or organism in an unedited state.