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Will gene-edited and other GM crops fail sustainable food systems?

13

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13.1 Introduction

Conventional agriculture^a is a major driver of climate change (Foley et al., 2005). Its intensive use of natural resources, synthetic fertilizers, and pesticides further degrades air, soil, and water quality and causes large-scale biodiversity loss (Foley et al., 2005; Horrigan, Lawrence, & Walker, 2002; Kremen & Merenlender, 2018; Pretty et al., 2000; Sánchez-Bayo & Wyckhuys, 2019; Tilman, 1998). Such assessments have driven wide agreement that conventional agriculture must become more sustainable. A transition to sustainable agriculture is also an essential component of sustainable food systems. However, there are very different views on how to improve the sustainability of agriculture while meeting food security goals (Godfray & Garnett, 2014; Holt-Giménez & Altieri, 2013; Kremen & Merenlender, 2018; McMichael & Schneider, 2011; Mercer, Perales, & Wainwright, 2012; Perfecto & Vandermeer, 2010; Zaidi et al., 2019).

The sustainability impact of biotech crops remains a key area of controversy. For good or ill, this impact is likely substantial. According to the most commonly cited source, in 2017 genetically modified (GM) crops were planted on 189.8 million ha in 24 countries (ISAAA, 2017^b). The majority of GM crops grown commercially are either herbicide tolerant (HT crops) or they produce GM pesticides originating from the bacterium *Bacillus thuringiensis*, an insect pathogen (*Bt* crops). The main HT and/or *Bt* commodity crops grown globally are soybean (94.1 million ha), maize (59.7 million ha), cotton (24.1 million ha), and canola (10.2 million ha) (ISAAA, 2017).

The narrow view of sustainability sees the role of agriculture as providing food security. It further equates food security with high yields (Latham, this volume). To obtain its yields, conventional agriculture combines large-scale monoculture cropping systems with the extensive use of off-farm inputs (e.g., hybrid seeds, agrochemicals, water, and fuel). Labor is replaced with mechanization. Soil fertility and pests are managed with synthetic fertilizers, insecticides, fungicides, and herbicides.

^a Conventional (also called industrial) agriculture includes input-heavy large-scale monoculture commodity cropping systems and confined animal feeding operations.

^b ISAAA (International Service for the Acquisition of Agri-biotech Applications) is funded by both government organizations and the biotech industry to promote the uptake of agricultural biotechnology products, including GM crops.

Hybrid seeds must be purchased each year. Consequently, increased sustainability is framed as increased monocrop yield/acre and/or a concomitant decrease in the use off-farm inputs. Biotechnology, specifically the use of GM crops (also called genetically engineered or bioengineered, e.g., transgenic, cisgenic, RNAi, or gene-edited crops), is often seen as necessary to achieve these sustainability goals (Ammann, 2005; Dibden, Gibbs, & Cocklin, 2013; Godfray & Garnett, 2014; Pretty, 2001). In this paradigm it is argued that, by increasing yields, GM crops can also benefit smallholder farming and sustainable agricultural systems (Holt-Giménez & Altieri, 2013; Mercer et al., 2012; Shelton, Hossain, Paranjape, & Azad, 2018).

The broad view of sustainability, in contrast, sees agriculture as intrinsically multifunctional, having diverse and interconnected environmental and social impacts (McIntyre et al., 2009). To be sustainable therefore agriculture must (1) provide food security and healthy diets *and* (2) support rural livelihoods and culture, while also reducing poverty and inequality *and* (3) increase biodiversity and environmental health, placing a strong emphasis on lessening climate change (Horrigan et al., 2002; Kremen & Merenlender, 2018; McMichael & Schneider, 2011). Within this paradigm, technologies and practices that support low-input small-scale agriculture, food and seed sovereignty, and local food systems are considered essential (Adhikari, 2014; Holt-Giménez & Altieri, 2013; Kremen & Merenlender, 2018; McIntyre et al., 2009). However, there are many different possible sustainable farming systems. These can include organic, agroecological, agroforestry, and traditional systems. What they have in common is the use of biodiversity to achieve multiple agricultural, environmental, and societal goals (Altieri, 1999; Thrupp, 2000; Wickson, Binimelis, & Herrero, 2016). For example, both soil health and pests are managed by increasing on-farm biodiversity via practices that include multispecies crop rotation, cover cropping, and intercropping, as well as push/pull, SRI^c and no-till techniques, and the incorporation of livestock and trees (Anderson, 2015; Hailu, Niassy, Zeyaur, Ochatum, & Subramanian, 2018; Kremen & Miles, 2012; Midega, Pittchar, Pickett, Hailu, & Khan, 2018; Pretty, 2001; Thakur, Uphoff, & Stoop, 2016; Zhang, Postma, York, & Lynch, 2014). Such techniques can drastically reduce the need for off-farm inputs, with the goal of eliminating them entirely (Nicholls, Altieri, & Vazquez, 2016). Within this broad agroecological paradigm of sustainability, GM crops are often seen as incompatible (Adhikari, 2014; Altieri, 2005; Barker, 2014; Fischer, 2016; Garibaldi et al., 2017; Kesavan & Swaminathan, 2018; Kremen & Miles, 2012; McIntyre et al., 2009; Pengue, 2005; Schütte et al., 2017; Wickson et al., 2016).

The availability of a wide diversity of crops and cultivars is an integral component of sustainable agriculture. Historically, farmer seed saving and selection created an enormous diversity of crop varieties with widely varying properties and adaptations (Villa, Maxted, Scholten, & Ford-Lloyd, 2005). The intention of plant breeding is to contribute to this diversity by producing crops with beneficial new trait combinations or characteristics. Conventional plant breeding achieves this via genetic crossing of sexually compatible plants, and the selection of offspring with the desired traits.

^c SRI stands for system of rice intensification, a set of practices that can reduce the use of water, seeds, and other inputs, while increasing soil biodiversity and improving yields.

Occasionally, conventional plant breeders use intentional mutagenesis, somaclonal mutation, or wide crosses to introduce novel traits (Wilson, Latham, & Steinbrecher, 2004). GM crop developers, in contrast, use a combination of lab-based techniques (e.g., recombinant DNA [rDNA] technology, tissue culture, and plant transformation [e.g., *Agrobacterium* infection or particle bombardment]) to introduce specific rDNA sequences, specifying novel traits, into crop plants (Barampuram & Zhang, 2011). GM techniques expand the range of traits available by conferring the ability to combine, alter, and transfer DNA from *any* organism (e.g., viruses, bacteria, fungi, mammals, nonfood plants) into a crop's genome (Wickson et al., 2016). A suite of new GM techniques (nGMs), including a variety of "gene editing" systems, has been developed for use in plants (Eckerstorfer, Heissenberger, Reichenbecher, Steinbrecher, & Waßmann, 2019). In contrast to standard GM techniques, gene editing techniques can target DNA integration and/or other modifications to specific regions of the genome (Fichtner, Castellanos, & Ülker, 2014). The claimed benefits of GM and nGM technologies are their ability (1) to transfer or alter specific sequences of DNA and (2) to introduce novel DNA modifications and traits that cannot be introduced via conventional plant breeding.

13.2 Impacts of HT and *Bt* crops

In theory, HT^d crops and *Bt*^e crops were intended to promote sustainable agriculture by (1) reducing overall pesticide use and (2) substituting safer pesticides (e.g., plant-produced *Bt* toxins or glyphosate herbicides) for more harmful ones (Ammann, 2005; Andow, 2010; Koch et al., 2015). HT crops have also been claimed to improve sustainability by facilitating the uptake of no-till agriculture.

In practice, however, the widespread use of *Bt* and HT crops has led to the problematic development of pest resistance, "superweeds," and secondary pests (Benbrook, 2018; Bonny, 2016; Carrière et al., 2016; García et al., 2019; Gould, Brown, & Kuzma, 2018; Kilman, 2010; Kranthi, 2016; Mortensen, Egan, Maxwell, Ryan, & Smith, 2012; Stone & Flachs, 2018; Tabashnik & Carrière, 2017). In response to these problems, farmers increased both insecticide and herbicide use. Some also increased tillage and other mechanical methods of weed control (Bonny, 2016; Green, 2014). The seed industry response has been to add multiple *Bt* pesticide and/or HT traits (stacked and

^d HT GM crops have one or more transgene(s) that specify a protein that either resists or detoxifies a specific herbicide. For example, the herbicide glyphosate targets an essential plant enzyme, 5-enolpyruvylshikimate-3-phosphate synthase (epsps), to cause lethality. Roundup Ready (RR) glyphosate-tolerant GM crops have a transgene that specifies a glyphosate tolerant version of the epsps enzyme.

^e *Bt* crops have one or more recombinant *cry* transgenes (e.g., *cry1Ab*, *cry3A*) inserted into their genome, each transgene specifying a different GM *Bt* toxin (Latham, Love, & Hilbeck, 2017). Plant-produced *Bt* toxins are derived from the natural toxins produced by the insect gut pathogen *Bacillus thuringiensis* (Sanchis, 2011). Different classes of *Bt* toxins are considered lethal to different orders of insects, and are used to target different plant pests (Carrière, Fabrick, & Tabashnik, 2016). For example, *B. thuringiensis* Cry1 toxins are thought to specifically target Lepidoptera (e.g., corn borers and cotton bollworms), while Cry3 toxins are believed to specifically target Coleoptera (e.g., corn rootworm, Colorado potato beetle).

pyramided traits^f) to each variety, and to develop new plant-produced pesticides (e.g., VIP protein toxins and RNAi-based insecticides) (Bøhn & Lövei, 2017; Carrière et al., 2016; Chakroun, Banyuls, Bel, Escriche, & Ferré, 2016; Gould et al., 2018).

In addition, the introduction of *Bt* and HT crops and their attendant pesticides has encouraged a variety of changes to farmer practice that themselves have had highly detrimental environmental impacts. First, the adoption of *Bt* and HT crops has undermined the use of integrated pest management (Gray, 2010) and sustainable techniques. They do so by substituting GM crop-produced and chemical pesticides for pesticide-free control measures that include tillage, short season crops, cover crops, crop rotation, and biological controls (Brainard, Haramoto, Williams, & Mirsky, 2013; Gutierrez, Ponti, Herren, Baumgärtner, & Kenmore, 2015; Kesavan & Malarvannan, 2010; LaCanne & Lundgren, 2018; Lang, Oehen, Ross, Bieri, & Steinbrich, 2015; Schütte et al., 2017; Stone & Flachs, 2018; Tooker, 2015). Second, growing *Bt* crops (a decision made before actual insect pressures are known) exposes the landscape, and consumers, to pesticide whether or not the targeted pest is a threat, and whether or not *Bt* toxins provide effective protection. Wide uptake of *Bt* crops is thus prophylactic pesticide use (Douglas & Tooker, 2015; Gray, 2010; Stone & Flachs, 2018; Tooker, 2015). Finally, HT crops have decreased biodiversity by encouraging simplified crop rotations and/or farming systems. They have also permitted unrestricted spraying of broad-spectrum herbicides throughout the growing season, further exacerbating biodiversity losses (Schreiner, 2009; Schütte et al., 2017). As another consequence, HT soybeans on the US market have a high level of glyphosate contamination (Bøhn et al., 2014).

Thus *Bt* and HT traits have exacerbated and expanded the pesticide treadmill (Altieri, 2000; Binimelis, Pengue, & Monterroso, 2009; Douglas & Tooker, 2015; Mortensen et al., 2012; Pengue, 2005; Stone & Flachs, 2018). The resulting “technology-facilitated pesticide treadmill” is described by Douglas and Tooker (2015):

Neonicotinoid seed treatments may also have “tagged along” with other technologies that were attractive to farmers. They are usually one component of larger packages, that, for instance in maize, can include germplasm (i.e., crop variety), up to eight transgenes, and up to six or more different seed treatments (fungicides, nematicides, and insecticides).

These well-documented outcomes indicate the adoption of HT and *Bt* crops is leading to dramatic increases in pesticide use over time, including the use of pesticides known to be extremely toxic such as neonicotinoids, glufosinate, 2,4-D, and dicamba (Douglas & Tooker, 2015; Mortensen et al., 2012; Schütte et al., 2017; Tooker, 2015). Increased herbicide use with HT crops has been repeatedly demonstrated in the scientific literature (Schütte et al., 2017). However, some authors claim that *Bt* crops can reduce pesticide use (e.g., Klümper & Qaim, 2014; Naranjo, 2009). Short-term

^f Stacked resistance traits are defined as multiple transgenes specifying tolerance to more than one herbicide (e.g., glyphosate, dicamba, and 2,4-d) and/or to more than one target pest (e.g., corn root worm and corn borer). Pyramided traits have more than one transgene targeting the same pest (e.g., Cry1Ab+Vip3A to target Lepidoptera).

studies (e.g., before resistance develops), or failure to quantify the amount of plant-produced *Bt* toxin(s) and/or seed coat insecticides, can account for these discrepancies (Benbrook, 2012; Douglas, 2016). When applied pesticides, GM crop-produced insecticides (e.g., Benbrook, 2012; Clark, Phillips, & Coats, 2005; Nguyen & Jehle, 2007; Saxena, Stewart, Altosaar, Shu, & Stotzky, 2004; U.S. Environmental Protection Agency, 2010; van der Hoeven, 2014), and seed coat pesticides are taken fully into account, both *Bt* and HT crops increase pesticide use in farming systems (e.g., Benbrook, 2012; Bøhn & Lövei, 2017; Bonny, 2016; Capellesso, Cazella, Schmitt Filho, Farley, & Martins, 2016; Douglas & Tooker, 2015; Heinemann, Massaro, Coray, Agapito-Tenfen, & Wen, 2014; Kranthi, 2016; Perry, Ciliberto, Hennessy, & Moschini, 2016; Yang, Iles, Yan, & Jolliffe, 2005).

13.2.1 Toxicity of GM crop-associated pesticides

Developers and US regulators of GM crops claim that *Bt* toxins and glyphosate are low-toxicity pesticides (Koch et al., 2015; Williams, Kroes, & Munro, 2000). However, for *Bt* crops, there is an ever-growing body of evidence showing *Bt* toxins and *Bt* plants have harmful off-target effects, including toward mammals, beneficial insects, and aquatic invertebrates (Andreassen et al., 2015; Hilbeck & Schmidt, 2006; Latham et al., 2017; Paula et al., 2014; Venter & Bøhn, 2016). Many researchers have pointed out the need for further biosafety research, in particular *in planta* studies and research on the sublethal and long-term effects of exposure to *Bt* crops (e.g., Andow, 2010; Arpaia et al., 2017; Hilbeck & Otto, 2015; Latham et al., 2017; Sanchis, 2011; Wolfenbarger, Naranjo, Lundgren, Bitzer, & Watrud, 2008). Similar concerns apply to glyphosate-based herbicides. For example, glyphosate and/or its formulations affect the composition of soil and gut microbiota and have negative effects on earthworms, beneficial insects, and aquatic organisms (Schütte et al., 2017; Sharma, Jha, & Reddy, 2018). They are also linked to cancer and chronic kidney disease in humans (e.g., Jayasumana, Gunatilake, & Senanayake, 2014; McHenry, 2018; Myers et al., 2016). Due to the large body of evidence documenting their harmful off-target impacts, coupled with significant research gaps, there is no scientific consensus that *Bt* toxins and glyphosate-based herbicides are low-toxicity pesticides (Ardekani & Shirzad, 2019; Hilbeck et al., 2015; Krimsky, 2015).

13.3 Unintended traits in GM crops

Regardless of the intended trait, GM technology is frequently acclaimed for its precision. In particular, the ability to introduce novel traits without the problem of “yield drag,” a problem that can complicate conventional plant breeding (Gepts, 2002). Yet, despite these claims, reports of unexpected and harmful unintended traits (UTs) in GM crops periodically surface in the media. For example, in 2012 various news outlets, including the *Wall Street Journal*, reported that the stalks of GM corn and soy were much tougher than those of conventional crops (Tita, 2012). The tougher GM stalks puncture tractor tires. This unexpected trait has both economic and environmental

costs, as farmers are forced to buy new and expensive reinforced tractor tires and/or replace tires more frequently. Like most such reports, the “tough stubble” trait has not been fully followed up or acknowledged in the scientific literature. Yet, it raises a host of important and neglected questions: (1) How precise and predictable is GM technology? (2) Do developers and regulators prevent GM crops with harmful UTs from reaching the market? (3) Are UTs an underappreciated barrier to sustainability?

A UT, sometimes called an unintended effect, is defined here as any significant difference, other than the intended GM trait, between a GM crop compared to a non-GM isogenic line. UTs thus include, for example, statistically significant differences in characters such as seed germination, weed suppression, pest resistance, drought tolerance, height, yield, and flowering time. UTs further include compositional differences in nutrients, toxins, and other biochemicals. Such UTs are often revealed by transcriptomic, proteomic, and metabolomic profiling studies (Cellini et al., 2004). Several reviewers have collected examples of a wide variety of UTs recorded in the scientific literature (Cellini et al., 2004; Haslberger, 2003; Kuiper, Kok, & Engel, 2003; Nature Institute, 2019; Ricroch, Bergé, & Kuntz, 2011). Nevertheless, the number of documented examples is much greater than those already collected, precluding a comprehensive review.

13.3.1 Precision and predictability

If GM technology was precise and predictable, biotechnologists would only need to create one GM plant, and this would be identical to the parent plant except for the intended new trait. However, biotechnologists instead produce many hundreds or even thousands of initial transformants.[§] For example, to identify a Roundup Ready (RR) wheat event for commercialization, Hu et al. (2003) used either *Agrobacterium* or the gene gun to introduce rDNA into over 98,000 plant tissue fragments. At the same time they tested a number of different transgenes, since it was not clear which would be the most effective in wheat. From their initial populations they selected over 1300 glyphosate-tolerant plants for further development, discarding the rest. Subsequent rounds of selection assessed Roundup resistance and basic agronomic performance. After four generations of such selection, six suitable events remained. Finally, after 3 years of “large-scale field trials,” one event was selected for commercialization and submitted to the US Department of Agriculture (USDA) for approval. The petition for deregulation of this event was subsequently withdrawn.

Research on large populations of initial transformants, created for the development of *Bt* rice (Shu et al., 2002), *Bt*, or blight-resistant potato (Davidson et al., 2004; Felcher, Douches, Kirk, Hammerschmidt, & Li, 2003), virus-resistant tobacco (Xu, Collins, Hunt, & Nielsen, 1999), and virus-resistant barley (Bregitzer, Halbert, & Lemaux, 1998), suggest similar problems for other GM crops and traits. Defects in basic agronomic traits such as yield, height, stem, and leaf morphology are frequent in regenerated GM plants, and many initial transformants exhibit multiple UTs. Even when only a few (from 2 to 22) traits are assessed, the proportion of initial transformants

[§] A transformant is a cell or an organism, such as a plant, into which foreign DNA has been introduced.

with UTs usually ranges between 20% and almost 100% (e.g., Bregitzer et al., 1998; Dale & McPartlan, 1992; Davidson et al., 2004; Felcher et al., 2003; Hoekema, Huisman, Molendijk, van den Elzen, & Cornelissen, 1989; Kumar, Rakow, & Downey, 1998; Shu et al., 2002; Vickers, Grof, Bonnett, Jackson, & Morgan, 2005).

Later in GM crop development, diverse UTs are still frequently identified, even after multiple rounds of selection. To take rice as a sample crop, decreased yield, seed size, or vigor have all been reported for different *Bt* rice lines (e.g., Bashir et al., 2004; Chen, Snow, Wang, & Lu, 2006; Jiang et al., 2018; Shu et al., 2002; Tu et al., 2000; Wang et al., 2012; Wei-xiang, Qing-fu, Hang, Xue-jun, & Wen-ming, 2004; Wu, Shu, Wang, Cui, & Xia, 2002), as have alterations to grain and straw quality (e.g., Bashir et al., 2004; Li et al., 2008; Wei-xiang et al., 2004; Wu et al., 2002). As well, height, yield, and developmental UTs have been documented for glufosinate-tolerant rice lines (Oard et al., 1996).

Additional examples of UTs are collected in Tables 13.1 and 13.2 of this review. These, combined with examples collected by other reviewers, confirm that UTs are not limited to any particular GM technique, trait, or plant species (Cellini et al., 2004; Haslberger, 2003; Kuiper et al., 2003; Nature Institute, 2019; Ricroch et al., 2011).

13.3.2 *UTs in commercial GM crops*

Commercial GM crops are considered “the best of the best” that GM plant breeding can offer. They undergo years of selection and development prior to “rigorous compositional, nutritional, and safety evaluations” and, in some cases, environmental risk assessments (Larkin & Harrigan, 2007). Finally, most GM crops currently grown have undergone some form of regulatory process before their commercial release or import was permitted (Davison, 2010; Pelletier, 2005). Nevertheless, Table 13.1 provides examples of some of the many UTs that have been identified in commercial GM crops. These UTs are documented in peer-reviewed papers and/or the petition submitted to USDA/APHIS (U.S. Department of Agriculture/Animal and Plant Health Inspection Service) to deregulate a particular crop or event in the United States. The examples given in Table 13.1 have been selected because they have implications for sustainability.

Important conclusions can be drawn from Table 13.1. First, it is not difficult to find examples of commercial crops with UTs. In fact, many commercial GM crops have multiple UTs. UTs documented for Mon810 maize, for example, include numerous compositional differences (including increased lignin and the presence of an allergen), increased moisture content, and negative impacts on beneficial soil organisms. Second, UTs have different origins. Some, such as the increased lignin levels associated with cry1Ab *Bt* maize, are likely pleiotropic effects of the transgene (i.e., the trait itself), as they are seen with many independent cry1Ab events. Others, such as the loss of resistance to root knot nematode in *Bt* Paymaster cotton, are event specific and likely due to mutational damage at or near the transgene insertion site (Colyer et al., 2000).

Third, many UTs commonly documented in commercial GM crops have had unequivocal negative impacts on sustainability. For example, high moisture content, as documented for MON810 and Bt11 maize, requires added energy during drying

Table 13.1 Examples of unintended traits in commercial HT, *Bt*, or virus-resistant GM crops.

GM crop	Transgene event (transgene name ^{a,b})	Intended trait	Unintended traits compared to non-GM parent or isogenic line (references)
<i>Bt</i> maize	Event Mon810 (cry1Ab)	Lepidopteran insect resistant (pesticidal)	<ul style="list-style-type: none"> • Increased lignin in stem (Flores, Saxena, & Stotzky, 2005; Poerschmann, Gathmann, Augustin, Langer, & Górecki, 2005; Saxena & Stotzky, 2001) • Altered sugar content, osmolytes, branched amino acids, and proteins (including truncated proteins and the presence of an allergen) in kernels (Barros et al., 2010; Manetti et al., 2006; Zolla, Rinalducci, Antonioli, & Righetti, 2008) • Decreased protozoan and nematode numbers, and drier rhizosphere soils (Griffiths et al., 2005; Höss et al., 2008) • Increased aphid susceptibility (Faria, Wäckers, Pritchard, Barrett, & Turlings, 2007) and thrip numbers (Bourguet et al., 2002) • Delay in seed and plant maturation (La Paz, Pla, Centeno, Vicient, & Puigdomènech, 2014) • Higher moisture content in whole plant and grain at harvest (Ma & Subedi, 2005) • Delayed decomposition of Mon810 maize plant residues (Flores et al., 2005; Stotzky, 2004)
<i>Bt</i> maize	Event Bt11 (cry1Ab)	Lepidopteran insect resistant (pesticidal)	<ul style="list-style-type: none"> • Increased lignin in stem (Flores et al., 2005; Saxena & Stotzky, 2001) • Increased aphid susceptibility (Faria et al., 2007) • Higher moisture content in the whole plant and grain at harvest (Ma & Subedi, 2005) • Detrimental impacts on corn root colonization by beneficial mycorrhizal fungi (Castaldini et al., 2005)
<i>Bt</i> maize	Event 176 (cry1Ab)	Lepidopteran insect resistant (pesticidal)	<ul style="list-style-type: none"> • Increased lignin in stem (Poerschmann et al., 2005; Saxena & Stotzky, 2001) • Increased aphid susceptibility (Faria et al., 2007) • Detrimental impacts on corn root colonization by beneficial mycorrhizal fungi (Castaldini et al., 2005)

Roundup Ready maize	Event NK603 (cp4 epsps)	Resistant to glyphosate herbicide	<ul style="list-style-type: none"> Decreased γ-tocopherol and inositol; increases in potentially toxic polyamines, e.g., <i>N</i>-acetyl-cadaverine (2.9-fold), <i>N</i>-acetylputrescine (1.8-fold), putrescine (2.7-fold), and cadaverine (28-fold) in kernel (Barros et al., 2010; Mesnage et al., 2016) Evidence of kidney and liver toxicity (Fagan, Traavik, & Bøhn, 2015) Unintended proteomic and plant defense-related phytohormone differences in leaves (Benevenuto et al., 2017) Statistically significant differences for ear height and days to 50% silking (USDA/APHIS petition 00-011-01p) Average maize yield for epsps glyphosate-tolerant GM maize varieties (such as NK603) decreased by 5.98 bushels per acre compared to conventional varieties (Shi, Chavas, & Lauer, 2013) Yield decrease of 7%–11% (Gordon, 2007; Nelson, Renner, & Hammerschmidt, 2002; Elmore et al., 2001; Benbrook, 1999; USDA/APHIS Petition P93–258-01) Note: grown extensively in major soy producing countries such as the United States, Brazil, and Argentina (e.g., over 93% of the US soybean crop is RR HT soy) (Oliveira & Hecht, 2016) 5% decrease in height (USDA/APHIS Petition 06-SB-167U; Horak et al., 2015) RR1 and RR2Y have similar yields (Mason, Walters, Galusha, Wilson, & Kmail, 2017)
Roundup Ready (RR1) soybean	Event 40–3–2 (cp4 epsps)	Resistant to glyphosate herbicide	
Genuity Roundup Ready 2 Yield (RR2Y) soybean	Event MON-89788-1 (cp4 epsps)	Resistant to glyphosate herbicide	
Virus-resistant squash	Event CZW-3 (three transgenes specifying coat proteins from CMV, ZYMV, and WMV2)	Resistant to three viruses affecting cucurbits	<ul style="list-style-type: none"> Beta-carotene decreased to 1.5%, iron decreased to 87%, and fat to 50%, of control levels (Table V, USDA/APHIS Petition no. 95-352-01p) Vitamin A levels increased twofold and sodium increased fourfold, compared to control lines (Table V, USDA/APHIS Petition no. 95-352-01p) Other unintended traits include differences in floral traits and altered bee visits compared to an isogenic line (Prendeville & Pilsen, 2009) Loss of resistance to golden nematode, a key trait present in its non-GM parent plant (Brodie, 2003; Brodie & Mai, 1989)
<i>Bt</i> potato Atlantic NewLeaf	Atlantic NewLeaf Clone 6 (cry3A)	Coleopteran insect resistant (pesticidal)	

Continued

Table 13.1 Continued

GM crop	Transgene event (transgene name ^{a,b})	Intended trait	Unintended traits compared to non-GM parent or isogenic line (references)
<i>Bt</i> cotton Paymaster	Event 15560BG (cry1Ac)	Lepidopteran insect resistant (pesticidal)	<ul style="list-style-type: none"> Loss of resistance to root knot nematode (Colyer, Kirkpatrick, Caldwell, & Vernon, 2000)
Bollgard <i>Bt</i> cotton, INGARD	Event: N/A (cry1Ac)	Lepidopteran insect resistant (pesticidal)	<ul style="list-style-type: none"> Several varieties showed increased susceptibility to <i>Fusarium</i> fungal disease (Kochman et al., 2000)
Chinese <i>Bt</i> cotton	Event: N/A (cry1Ac)	Lepidopteran insect resistant (pesticidal)	<ul style="list-style-type: none"> Two varieties had decreased resistance to <i>Fusarium oxysporum</i> fungal disease compared to controls (Li et al., 2009)
<i>Bt</i> cotton	Event GK97 (N/A)	Lepidopteran insect resistant (pesticidal)	<ul style="list-style-type: none"> Altered composition of root exudates (Li et al., 2009) Quantitative and qualitative differences in volatiles (Yan et al., 2004)
Roundup Ready oilseed rape	<i>Brassica napus</i> cv. Quest Event: N/A (cp4 epsps)	Resistant to glyphosate herbicide	<ul style="list-style-type: none"> Altered diversity of root-endophytic bacteria (Siciliano & Germida, 1999; Siciliano, Theoret, De Freitas, Hucl, & Germida, 1998)
HT winter rape	Events: N/A Two cultivars: Falcon pat (pat) and cultivar ArtusLL (N/A)	Resistant to glufosinate herbicide	<ul style="list-style-type: none"> Altered flowering in both cultivars (Pierre et al., 2003)

The UTs listed have implications for sustainability, for example, via decreased yields or potential impacts on ecological interactions.

Bt, *Bacillus thuringiensis*; *CMV*, cucumber mosaic cucumovirus; *epsps*, 5-enolpyruvylshikimate-3-phosphate synthase; *GM*, genetically modified; *HT*, herbicide tolerant; *WMV*, watermelon mosaic potyvirus 2; *ZYMV*, zucchini yellow mosaic potyvirus.

^a "N/A" indicates no information was provided in the reference.

^b Many transgenic events also include additional marker genes, which are usually recombinant antibiotic or herbicide resistance genes. Associated marker genes are not noted in most references and have not been included in this table.

Table 13.2 Examples of unintended traits (UTs) identified in crops having “complex” genetically modified traits intended to improve their agronomic performance, resistance to abiotic stress, or nutritional value.

Crop	Intended trait	Unintended traits compared to non-GM parent or isogenic line
Potato	Increased tuber dormancy	Lower tuber yield and/or fewer tubers per plant (Marmioli et al., 2000)
Potato	Reduced browning	Unintended alterations to glycoalkaloid and sesquiterpene levels (Matthews, Jones, Gans, Coates, & Smith, 2005)
Potato	High amylose	Large unintended increase in phosphorus; altered sucrose levels, yield, and growth (Hofvander, Andersson, Larsson, & Larsson, 2004)
Cotton	Increased salt tolerance	Decreased seed yield under normal growth conditions (Zhang et al., 2009)
Buckwheat	Increased salt tolerance	Unintended agronomic and compositional changes when grown under greenhouse conditions (Chen, Zhang, & Xu, 2008)
Rice and barley	Increased salt tolerance	Numerous unexpected metabolic changes in both rice and barley (Jacobs, Lunde, Bacic, Tester, & Roessner, 2007)
Tomato	Increased provitamin A levels	Reduced lycopene (Römer et al., 2000)
Tomato	Novel flavonoids	Decreased seed set, color changes, parthenocarpy, and enzymatic differences (Schijlen et al., 2006)
Maize	Increased lysine content	Agronomic and metabolic UTs (Bicar et al., 2008)
Rice	Increased tryptophan levels	Agronomic and metabolic UTs (Wakasa et al., 2006)

(Ma & Subedi, 2005). UTs such as a loss of pest resistance or decreased yield potential undermine sustainability, particularly when farmers use more external inputs (e.g., fuel, pesticides, fertilizer, water) to maintain yields. Table 13.1 includes the large yield decreases documented for RR soybeans (7%–11% decrease), glyphosate HT maize (5.98 bushels/acre decrease), and corn root worm-protected *Bt* maize (12.22 bushels/acre decrease) (Gordon, 2007; Shi et al., 2013). Loss of pest or pathogen resistance documented in Table 13.1, includes increased aphid and/or thrip numbers on *Bt* maize varieties, loss of nematode resistance in Atlantic NewLeaf *Bt* potato and Paymaster *Bt* cotton, and decreased resistance to *Fusarium* fungal disease observed with various *Bt* cotton varieties (Bourguet et al., 2002; Brodie, 2003; Colyer et al., 2000; Faria et al., 2007; Li et al., 2009). Table 13.1 thus illustrates that commercial GM commodity crops, many grown on millions of acres worldwide, frequently have detrimental UTs, in addition to the “tough stalks” of HT and *Bt* crops, UTs that contribute to their large and negative environmental impacts.

Nevertheless, many biotechnologists tend to dismiss UTs as unimportant, even when they are identified in commercial varieties (e.g., Fox, Morrison-Saunders, & Katscherian, 2006; Larkin & Harrigan, 2007; Ricroch et al., 2011; Shepherd, McNicol, Razzo, Taylor, & Davies, 2006; Sidhu et al., 2000). This was the case with the yield loss UT documented for RR soybean. In their regulatory petition to the USDA, the developers of RR soybean claimed they would improve yields through further breeding, yet they were never able to do so (USDA/APHIS, Petition P93–258-01, 2020). Likewise, large and statistically significant compositional UTs in CZW3 squash were also dismissed, rather than interpreted as a red flag indicating a need for further risk assessment, or for rejection of that particular event or crop (USDA/APHIS Petition 95–352-01p). Yet, small and large compositional UTs, such as quantitative or qualitative alterations to metabolites, nutrients, or potential toxins, can negatively impact ecological interactions (Arpaia et al., 2017; Li et al., 2009; Mesnage et al., 2016; Venter & Bøhn, 2016) and/or food or feed safety (Haslberger, 2003; Pelletier, 2005; Schubert, 2008), traits essential to sustainability. Statistically significant differences seen under one environment or in one field trial, but not others, are also routinely dismissed. However, transgenes may be prone to large transgene \times environment interactions (Zeller, Kalinina, Brunner, Keller, & Schmid, 2010). Therefore UTs seen only under specific conditions should also be considered as a starting point for more risk assessment, as they could indicate a defect in environmental response or other significant problems (Agapito-Tenfen, Guerra, Wikmark, & Nodari, 2013).

It is important to emphasize the examples in Table 13.1 are not exhaustive of UTs that have been documented in commercial GM crops. A number of factors further combine to make it likely that the publicly available data seriously underestimate the number of commercial lines with UTs and the number of UTs in each commercial line. Many important sustainability traits, such as increased outcrossing, seed dormancy or seed-bank persistence, might never be assessed, despite their potential for negative impacts (e.g., Altieri, 2005; Bergelson, Purrington, & Wichmann, 1998; Linder, 1998; Linder & Schmitt, 1995). Other limitations for commercial GM crops include the lack of standardization for compositional studies, a lack of -omic analyses, the use of inadequate or inappropriate test conditions for many lab and field trials (e.g., inappropriate organisms or life stage tested for toxicity, inadequate distances between field plots) and a lack of studies on the long-term and sublethal effects of GM crops and products (Arpaia et al., 2017; Booij, 2014; Hilbeck, Meier, & Trtikova, 2012; Pelletier, 2005; Schubert, 2008).

In addition, the proprietary nature of GM crops acts to restrict independent research (Waltz, 2009). Universities and funders also do not encourage research that could find harm from GM crops, and findings of harm are often heavily contested or even suppressed (Fagan et al., 2015; Peekhaus, 2010; Waltz, 2009). Consequently, most commercialized GM crops have undergone little or no independent testing or risk assessment that could identify UTs (Diels, Cunha, Manaia, Sabugosa-Madeira, & Silva, 2011; Seralini, Mesnage, Defarge, & de Vendômois, 2014).

In summary, UTs are frequent, if not ubiquitous, in all crops developed using standard GM techniques, including commercial GM varieties. These UTs frequently have a negative impact on sustainability, making GM crops an inappropriate choice for sustainable agriculture and food systems (Kesavan & Swaminathan, 2018).

13.3.3 *Standard GM techniques contribute to UTs*

UTs can arise from unintended effects of the transgene (or accompanying selectable marker genes). However, the techniques used to produce a GM crop can also give rise to UTs (Wilson, Latham, & Steinbrecher, 2006).

Transgenes are introduced into a plant cell, usually via infection with *Agrobacterium*, or else a “gene gun” is used to bombard plant cells with DNA-coated particles. The transgene subsequently integrates into damaged regions of the plant genome, via the plant’s natural DNA repair mechanisms. The genomic location of transgene integration is therefore uncontrolled, and differs for each independent integration event. Modified plant cells are then regenerated back into whole plants via tissue culture. Regenerated plants with one or more transgenic events are selected (often with the aid of a cotransferred marker gene that specifies antibiotic or herbicide resistance) for further analysis.

Transgene insertion thus inevitably disrupts the endogenous plant genome. Furthermore, *Agrobacterium* infection, particle bombardment, and tissue culture have all been shown to be highly mutagenic. Together they can produce many thousands of mutations. These mutations can be at, or linked to, the site of transgene integration, and also spread throughout the genome (Wilson et al., 2006). Such mutations include base pair changes, large and small DNA insertions and deletions, large-scale genome rearrangements, as well as unintended integration of bacterial chromosomal DNA, vector DNA, multiple transgenes, and transgene fragments. Thus, the mutagenicity of GM techniques contributes to the frequency and variety of UTs documented in GM crops (Wilson et al., 2006). In some cases UTs can be removed via genetic recombination (outcrossing or backcrossing). However, UTs genetically linked to the transgene insertion site will be difficult if not impossible to separate from the desired trait. UTs are an even greater problem for commercial crops that are propagated clonally or are otherwise difficult or impossible to cross. These include potato, banana, cassava, and most tree crops.

13.4 **New GM traits and techniques**

The UTs described in previous sections were identified in GM plants engineered for a very limited number of traits: pest resistance, virus resistance, and/or herbicide tolerance. These are simple traits, specified by single transgenes whose novel products were not intended to alter normal plant functions, structures, or biochemical pathways.

For complex traits with the potential to benefit sustainable agriculture, such as increased tolerance to drought, salt, heat, or flood, intentionally altered levels of specific nutrients, or increased yield, UTs are likely to be an even greater obstacle (e.g., Flowers & Yeo, 1995; Kollist et al., 2019). Table 13.2 lists some of the many documented examples of GM crops with such complex traits that also exhibit UTs.

13.4.1 *Complex GM traits have a history of failure*

Despite receiving frequent and positive media attention, most attempts to develop commercial GM crops with complex GM traits have failed. At best they have lagged

far behind conventional plant breeding in producing viable products (e.g., [Barker, 2014](#); [Gilbert, 2016](#); [McFadden, Smith, Wechsler, & Wallander, 2019](#); [Stone & Glover, 2011, 2017](#)).

It is only recently that an extremely limited number of GM crops with complex traits have become commercially available (e.g., [McFadden et al., 2019](#); [Waltz, 2015](#)). However, despite the high risk of UTs, these new GM crops have undergone even less independent research, risk assessment, and regulatory scrutiny than previous commercialized GM crops ([Camacho, Van Deynze, Chi-Ham, & Bennett, 2014](#); [Waltz, 2016, 2018](#)). In fact, for “drought-tolerant” soybean HB4, the developers themselves admit they do not understand the mechanism of action behind their trait ([Waltz, 2015](#)).

13.4.2 Golden Rice case study

Golden Rice is a widely cited example of a nutritionally enhanced GM crop ([Bollinedi et al., 2014](#)). Unusually, a significant amount of research on Golden Rice has been published in the scientific literature. Golden Rice is thus useful as a case study of a GM trait that could theoretically benefit sustainable agriculture.

Golden Rice varieties contain two transgenes specifying enzymes in the β -carotene biosynthesis pathway ([Bollinedi et al., 2014](#); [Ye et al., 2000](#)). In theory, the targeted production of these enzymes in the rice endosperm will increase grain levels of β -carotene (provitamin A) ([Dubock, 2014](#)).

Since the first Golden Rice paper was published in 2000, public and private sector researchers have produced many iterations of Golden Rice, each one intended to further increase the levels of β -carotene in the rice grain ([Bollinedi et al., 2014](#)). Syngenta donated six of its GR2 events for public sector use ([Bollinedi et al., 2014](#)). The International Rice Research Institute (IRRI) has used these in breeding efforts targeted to countries deemed to have populations with high levels of vitamin A deficiency ([Bollinedi et al., 2014](#); [IRRI, 2019](#); [Stone & Glover, 2017](#)). Two Golden Rice events, GR2-R1 and GR2E, have been the subjects of the most research and development (e.g., [Bollinedi et al., 2017, 2019](#); [Paine et al., 2005](#); [Schaub et al., 2017](#)).

13.4.2.1 The GR2-R1 event causes agronomic defects, including dramatic yield loss

For many years, the GR2-R1 event was the focus of Golden Rice breeding efforts ([Bollinedi et al., 2017](#); [Stone & Glover, 2017](#)). GR2-R1 lines, however, gave consistently low yields ([Dubock, 2014](#); [Stone & Glover, 2017](#)). In addition, Indian researchers documented other UTs in GR2-R1, including dwarfism, bushy stature, pale green leaves, root defects, late flowering, and low fertility ([Bollinedi et al., 2017](#)).

At least two underlying defects contribute to the UTs observed in GR2-R1 rice. The first pertains to the introduced DNA itself. In GR2-R1 plants the enzymes specified by the transgenes are active in other tissues apart from the grain ([Bollinedi et al., 2017](#)). This indicates the failure of the GR2 transgene regulatory sequences to function as intended, at least in GR2-R1 ([Paine et al., 2005](#)). The second defect was discovered when the Indian researchers sequenced the site of GR2-R1 integration. In GR2-R1,

the integrated transgene disrupts a native gene, called *OsAux1*, that specifies an auxin transport protein (Bollinedi et al., 2017). Auxins are plant hormones with vital functions in growth and behavior.

Both the regulatory and the insertion-site defects are predicted to impact several additional plant hormones, all with important roles in plant growth and development. These include abscisic acid, gibberellin, and cytokinin. Indeed, the researchers found levels of these three hormones were altered in leaves, stems, and flowering parts of GR2-R1 rice, as compared to non-GM isogenic lines (Bollinedi et al., 2017). In light of its many UTs and inherent molecular defects, efforts to further develop GR2-R1 were abandoned.

13.4.2.2 GR2E: Low levels of β -carotene in grain

As GR2-R1's defects became clear, a second event, GR2E, was incorporated into IRRI's Golden Rice breeding program (Dubock, 2014). However, the effectiveness of the Golden Rice trait to produce provitamin A varies widely between events (Bollinedi et al., 2019; Paine et al., 2005). Of Syngenta's six GR2 events, GR2E has the lowest β -carotene levels (Bollinedi et al., 2014; Paine et al., 2005).

While other, sometimes higher, measurements exist in the scientific and regulatory literature (Bollinedi et al., 2019; FSANZ, 2017; Paine et al., 2005; Schaub et al., 2017), the data submitted to regulators worldwide gave the β -carotene level of GR2E rice as only 3.5 $\mu\text{g/g}$ when milled and 0.5–2.35 $\mu\text{g/g}$ when unmilled (FDA, 2018a, 2018b).

13.4.2.3 Golden Rice: β -carotene degrades rapidly in storage

Two different research groups have reported that β -carotene levels in GR2E rice grains decrease rapidly in storage (Bollinedi et al., 2019; Schaub et al., 2017). After 3 weeks of storage, Golden Rice GR2E retained only 60% of its original levels. After 10 weeks, only 13% remained (Schaub et al., 2017). The second paper reported similar results, this time for both GR2E and GR2-R1 (Bollinedi et al., 2019). For GR2-R1, rapid degradation was shown to occur in several different genetic backgrounds. Cooking was shown to further decrease β -carotene levels (Bollinedi et al., 2019). Together, these results suggest that rapid degradation of β -carotene during normal storage and cooking conditions is a general problem of Golden Rice varieties.

13.4.2.4 Golden Rice: Commercialization despite missing benefit and risk assessment?

Agronomic and biosafety UTs in Golden Rice are likely to arise from two aspects of the trait. First, UTs can arise from unintended alterations to the many biosynthetic pathways that intersect with the β -carotene biosynthesis pathway, as demonstrated in GR2-R1. These intersecting pathways produce a wide variety of compounds in addition to plant hormones, including volatiles, other carotenoids, and unknown signaling molecules (DellaPenna & Pogson, 2006). Such UTs in the grain might impact nutrition, toxicity, seed dormancy, germination, and fertility, for example.

Second, the rapid breakdown of β -carotene in the grain raises questions about the level and biosafety of the breakdown products (Schaub et al., 2017).

However, despite the high probability of UTs, there is currently a complete absence of -omic data or other applicable research for GR2E. Furthermore, key human efficacy and safety studies are still lacking for targeted populations (Schubert, 2008; Stone & Glover, 2017; Then & Bauer-Panskus, 2018). Yet, regulators in Australia, the United States, and Canada have accepted developer's biosafety claims for GR2E (IRRI, 2019).

The data on Golden Rice thus conflict with proponents' claims that critics and overregulation are responsible for the ongoing failure of Golden Rice (Dubock, 2014; Lee & Krimsky, 2016; Stone & Glover, 2017). Instead, the available data suggest the commercialization of Golden Rice has been consistently hindered by technical difficulties inherent to GM plant breeding. Furthermore, the current leading candidate, GR2E, is unlikely to make a useful contribution to the stated humanitarian goal of helping to alleviate vitamin A deficiency in target populations. This is due in part to the low initial levels, and subsequent rapid degradation, of β -carotene in GR2E grains. Its commercialization would, however, introduce unnecessary agronomic and biosafety risks into the food system. Vacuum packaging of Golden Rice, which has been suggested to slow β -carotene degradation, would further undermine food system sustainability (Bollinedi et al., 2019).

13.4.2.5 Golden Rice: Illuminating the failures of GM plant breeding

The development of Golden Rice, a complex GM trait, exemplifies many of the inherent technical challenges faced by all GM plant breeders. These include (1) the imprecision and mutagenic nature of the techniques used to introduce GM traits, (2) inadequate scientific understanding of the biological processes underlying the relationships between transgenes and genome structure and function, and (3) the limited scientific understanding of the relationships between genes and traits, and how these are impacted by developmental and/or environmental factors.

These technical difficulties combine to make GM plant breeding prone to UTs and, ultimately, failure. The history of Golden Rice development suggests that the production of safe and robust crop varieties that successfully express complex GM traits, those most likely to be useful for sustainable agriculture, is likely to be even more problematic.

Golden Rice further highlights the overall institutional failure of regulators to implement adequate risk assessment and regulation for GM crops. As many researchers have already noted, more stringent regulation is needed (1) to ensure GM traits and crops fulfill their stated purpose and also (2) to safeguard the food system and the environment (Fox et al., 2006; Freese & Schubert, 2004; Heinemann, Agapito-Tenfen, & Carman, 2013; Heinemann, Kurenbach, & Quist, 2011; Hilbeck et al., 2015; Hilbeck & Otto, 2015; Latham et al., 2017; Mandel, 2003; Modonesi & Gusmeroli, 2018; Pelletier, 2005, 2006; Schubert, 2008; Venter & Bøhn, 2016; Wilson et al., 2006).

13.4.3 Are new GM techniques more precise?

Biotechnologists now claim that a new generation of genome modification techniques (nGMs) is essential to sustainably increase food production (Stone, 2017; Zaidi et al., 2019). These nGMs include cisgenesis/intragenesis^h and RNAi.ⁱ For the specific risks arising from intragenic, cisgenic, and RNAi-based traits, the reader is referred to other reviews (Casacuberta et al., 2015; Eckerstorfer et al., 2019; Gelinsky & Hilbeck, 2018; Heinemann et al., 2013; Lundgren & Duan, 2013; Senthil-Kumar & Mysore, 2011).

The most recently developed nGMs for plants, and by far the most discussed, include techniques that are referred to as “gene editing” (Agapito-Tenfen, Okoli, Bernstein, Wikmark, & Myhr, 2018; Casacuberta et al., 2015; Eckerstorfer et al., 2019; Hou, Atlihan, & Lu, 2014; Lusser & Davies, 2013). Gene editing is a disparate family of techniques that include oligonucleotide-directed mutagenesis (ODM),^j and/or the use of site-directed nucleases such as meganucleases, TALENs,^k ZFN,^l and CRISPR/Cas9^m. Of these, CRISPR/Cas9 is the most widely used (Fichtner et al., 2014; Lusser & Davies, 2013; Sauer et al., 2016). The claimed benefit of gene editing is that genome modifications can be precisely targeted to specific genomic locations.

A very wide variety of genome modifications can be intentionally introduced via gene editing (Ahmad, Rahman, Mukhtar, Zafar, & Zhang, 2019; Eckerstorfer et al., 2019; Fichtner et al., 2014; Lusser & Davies, 2013; Puchta, 2017). These extend from single base-pair changes to large-scale insertions or deletions of DNA. Insertions could include transgenes, cisgenes, RNAi-based traits, regulatory sequences, or multiple transgenes. CRISPR/Cas9 can further be used to create multiple changes at the same time, in a single gene or at multiple sites in the genome. Called multiplexing, this technique can be used, for example, to mutate or knock out several different members of a gene family (Fichtner et al., 2014).

A key question for sustainability is whether gene editing, which is claimed to be far more precise than standard GM, can introduce beneficial traits without the introduction of UTs. While the publicly available data for edited crop plants is still extremely

^h Cisgenic/intragenic traits utilize only DNA derived from the host plant or a cross-compatible plant. In this they differ from standard transgenic traits that routinely utilize DNA from distantly related organisms.

ⁱ RNAi-based traits specify double-stranded RNA molecules that trigger RNA interference (RNAi) pathways. This disrupts the cellular processes that connect specific genes with the production of specific proteins (Heinemann et al., 2013). The target of the RNAi is specified by the nucleotide sequence of the RNAi molecule.

^j ODM is a generic term for a wide range of different methodologies that use synthetic oligonucleotides to introduce a specific mutation at a particular site in the plant genome (ACRE, 2011). The oligonucleotides used for ODM are homologous to the targeted endogenous plant sequences except for the site of the intended mutation.

^k TALENs stands for transcription activator-like effector nucleases. TALENs are engineered nucleases that cut DNA at specific target sequences.

^l ZFN stands for zinc finger nuclease. ZFNs are engineered DNA-binding proteins that cut DNA at specific target sequences.

^m CRISPR stands for clustered regularly interspaced short palindromic repeats. In the CRISPR/Cas system, the engineered CRISPR RNA acts as a “guide” RNA that combines with a protein, for example, the Cas9 nuclease, and targets it to a specific DNA sequence.

limited, there are reasons to expect that plant gene editing methods are also prone to introducing UTs.

First, virtually all gene editing protocols utilize standard GM techniques, i.e., tissue culture and either *Agrobacterium* infection or the gene gun (Ahmad et al., 2019; Ding, Li, Chen, & Xie, 2016; Eckerstorfer et al., 2019). These techniques serve to introduce the gene editing reagents, which can include DNA, RNA, protein, or oligonucleotides, into plant cells. For example, *Agrobacterium* infection can be used to introduce DNA that specifies the CRISPR RNA guide sequence and the Cas9 nuclease, either transiently or via DNA integration. However, as discussed previously, tissue culture, *Agrobacterium* infection, and the gene gun are highly mutagenic, able to introduce thousands of mutations throughout the genome (Wilson et al., 2006). Proposed alternative methods, such as direct uptake of DNA-free reagents into protoplasts, may be less mutagenic and thus less likely to introduce UTs. However, this assumption remains to be tested experimentally. Furthermore, such methods are currently not available for most crop species (Ding et al., 2016).

Second, new evidence from both animals and plants indicates that gene editing itself can result in unintended mutations at or near the target site. These include the insertion of vector, bacterial, and other superfluous DNA, and the unintended introduction of large DNA deletions and rearrangements (Biswas et al., 2020; Kosicki, Tomberg, & Bradley, 2018; Li et al., 2015; Norris et al., 2019; Ono et al., 2015).

Third, new research from animals suggests that even precise and intended edits can cause frequent on-target mRNA misregulation (Sharpe & Cooper, 2017; Tuladhar et al., 2019). These include “exon skipping” and unintentionally altered RNA splicing. Both can produce new protein coding sequences with the potential to result in UTs.

Fourth, it has been shown in both plants and animals that gene editing reagents can make cuts at unintended sites in the genome. These cuts can result in off-target edits and potentially UTs (Ahmad et al., 2019; Biswas et al., 2020; Fichtner et al., 2014; Jin et al., 2019).

Fifth, gene editing is being applied to situations where researchers have little prior research to guide them. Thus some researchers suggest gene editing can be used for “fast tracking development of underutilized species or perhaps wild species into widely adapted options to help improve global food security” (Van Eck, 2018). Additionally, it is being adapted to target regions of the genome that, during conventional breeding, are usually protected from genomic change (Kawall, 2019). The results of multiplexing would also be difficult if not impossible to introduce via conventional plant breeding (Kawall, 2019). Such novel uses of gene editing will likely increase the already high likelihood of introducing UTs.

These observations support the conclusion that plant gene editing outcomes are imprecise and unpredictable, and that, depending on the combination of techniques used, gene editing can be highly mutagenic. However, because gene editing is a new field of research, particularly for plants, there are still many knowledge gaps (Ahmad et al., 2019; Schindele, Wolter, & Puchta, 2018). Lacking are whole genome sequences for gene-edited crop plants and nonedited comparators. Also lacking are systematic analyses of UTs in gene-edited crops. The knowledge gaps are especially large with regard to the unintended effects of different types of gene editing techniques and different

types of edits, particularly in crops being developed for commercial use. That UTs in gene-edited organisms will be frequent, however, is suggested by a recent news report. This described gene-edited animals with UTs that ranged from spotted fleece to big tongues, extra vertebrae, sickness, and death (Rana & Craymer, 2018). Nevertheless, most plant gene editing papers have not systematically tested for UTs. However, one group found that CRISPR-Cas9-generated promoter variants of the maize ARGOS8 gene, intended to improve maize grain yield under drought stress, exhibited UTs, including statistically significant differences in plant height, ear height, and grain moisture (Shi et al., 2017).

Therefore while biotechnologists frequently claim, “CRISPR in agriculture should be best considered as simply a ‘new breeding method’ that can produce identical results to conventional methods in a much more predictable, faster and even cheaper manner” (Gao, 2018), it is clear that CRISPR and other gene editing techniques are more similar to GM than conventional plant breeding due to the use of plant transformation techniques to introduce DNA or other reagents, the use of tissue culture, and the potential for exogenous DNA insertion (Eckerstorfer et al., 2019; Kawall, 2019). Like standard GM, the number and type of UTs introduced using gene editing will depend, in part, on the new trait being introduced and, in part, on the unintended effects wrought on the genome by the techniques themselves. All benefits, hazards, and risks must therefore be assessed experimentally on a case-by-case basis for each independently derived nGM trait and crop (Biswas et al., 2020; Eckerstorfer et al., 2019; Gelinsky & Hilbeck, 2018; Hilbeck et al., 2015). This should include whole genome sequencing comparisons with an isogenic line and -omic analyses.

13.5 Sustainable agriculture and plant breeding

As discussed, the introduction of GM crops has not made conventional agriculture more sustainable. However, the failures of GM plant breeding, and of GM agriculture more broadly, provide insight into the changes necessary for a transition to sustainable systems.

An important insight comes from the experience of farmers who have turned to regenerative agriculture. These farmers replace GM crops and their high-input management systems with some combination of sustainable practices that increase biodiversity, decrease topsoil loss, and increase natural soil fertility (e.g., complex cover crops, intercropping, multiyear multicrop rotations, GM-free no-till agriculture, the reintroduction of livestock). Research suggests regenerative farming leads to increased financial and environmental sustainability (LaCanne & Lundgren, 2018). Financial benefits occur primarily through the lower cost of conventional seeds, and because improved soils and decreased pest pressures reduce the need for costly and polluting inputs, including synthetic pesticides and fertilizers. In other words, the introduction of new traits or cultivars is only one of the many components necessary to improve sustainability. Conversely, to support sustainable agriculture, plant breeders must develop traits specifically tailored to, and selected within, low-input sustainable systems (Murphy, Campbell, Lyon, & Jones, 2007; van Bueren et al., 2011).

To date, however, the vast majority of conventional crop varieties used within organic and other sustainable systems have been bred for and selected within conventional systems (Murphy et al., 2007; van Bueren et al., 2011). But varieties that give high yields or perform best in conventional systems do not always do best in organic systems (Murphy et al., 2007; van Bueren et al., 2011). This is because pests and pathogens of primary concern for resistance breeding differ between the two systems. Weeds also are differentially problematic, since herbicides are not used in organic systems (van Bueren et al., 2011). Additionally, non-GM cultivars developed for conventional systems can have extremely negative trade-offs for sustainability. For example, semidwarf cereal varieties, introduced to prevent lodging, have a variety of UTs, such as decreased mineral nutrition and protein content; decreased root size and depth; decreased disease resistance and nutrient use efficiency; and poorer weed suppression (Marles, 2017; van Bueren et al., 2011). These defects can be masked in high-input systems. Thus crops and traits bred specifically for sustainable systems could greatly benefit both the yields and the performance of sustainable systems.

13.5.1 Traits for sustainable systems

Researchers have identified a number of characters and traits that are likely to be of general importance when breeding cultivars for organic agriculture and other sustainable systems (van Bueren et al., 2011). These include increased nutrient-use efficiency (vigorous root systems or root exudates that promote beneficial symbiosis with soil microbiota) or uptake (increase in fine roots); resistance to fungal and bacterial disease; insect resistance (e.g., changes in life history, gross morphology, physical characteristics, or metabolism to promote resistance; Carmona, Lajeunesse, & Johnson, 2011); improved ability to compete against weeds; improved tolerance to abiotic stressors; and quality improvements, including improved nutritional value. Modern conventional crop varieties, and, in particular, landraces or farmers varieties and their wild relatives, all provide valuable sources of variation when breeding for sustainable systems (Deb, 2014; Dwivedi et al., 2016; van Bueren et al., 2011).

The usefulness and impact of a particular trait will depend on the specific cropping system and the crop species (van Bueren et al., 2011). For example, within no-till systems, weeds are potential problems, as are deep planting depths and soil moisture (Joshi, Chand, Arun, Singh, & Ortiz, 2007). Consequently, useful traits for herbicide-free no-till systems include those leading to faster seed emergence (or other traits that increase competitiveness against weeds); faster (or in some cases slower) residue decomposition; the ability to germinate when deep seeded; and resistance to mechanical weeding (Joshi et al., 2007; van Bueren et al., 2011). Other traits with potential benefits include resistance to pests and pathogens that survive on crop residues and resistance to phytotoxic organic acids released by some residues (Joshi et al., 2007).

The priorities for cultivars intended for use in polyculture systems (e.g., the ancient “three sisters” maize/bean/squash system of the Americas, cereal and legume systems in Africa or Asia, or covercrop polycultures) differ from those of no-till. Useful traits tend to promote complementarity rather than competition between the crops. For example, researchers found maize, squash, and beans grown in a polyculture have

a niche complementarity-dependent yield advantage (as compared to being grown in monoculture), likely arising from differences in root nutrient foraging strategies (Zhang et al., 2014). Therefore traits that promote root or shoot plasticity could be explored for polyculture crops (Zhang et al., 2014). On the other hand, allelopathic traits, as suggested for no-till systems to promote weed suppression (van Bueren et al., 2011), might negatively impact polyculture symbioses.

Natural ecosystems can suggest further traits. For example, prairies have inspired efforts to breed perennial grains (e.g., wheat) and sunflowers (Piper, 1993). A recent review suggests perennial grains, which require well-developed root systems, have lower input requirements, and can support multifunctional sustainable systems. For example, they can protect and improve soil on sloped land, when intercropped with annuals or perennials, and/or in grazing systems or long-term rotations (Ryan et al., 2018).

13.5.2 Sustainable breeding: Considerations and strategies

For plant breeders to support the kinds of food and seed sovereignty goals embodied by agroecological farming systems, they need to be responsive to farmer and community needs. This in turn requires breeding strategies that are flexible and easily adapted to differences in environment, scale, sustainable practice, and markets. Flexibility and adaptability are essential given the large variety of low-input and sustainable systems possible and the widely varying needs of local food systems. To these can be added the growing uncertainty generated by climate change.

Participatory plant breeding strategies, where breeders collaborate with farmers (and sometimes others, including consumers and traditional farmer-focused breeding companies) are a promising method to achieve these multiple outcomes (Ceccarelli & Grando, 2019; Cleveland, Daniela, & Smith, 2000; Mercer et al., 2012; Murphy, Lammer, Lyon, Carter, & Jones, 2005; van Bueren et al., 2011). Involving farmers at the start of the breeding program broadens understanding and should better ensure varieties provide farmer-preferred traits. Holding variety trials in farmers' fields, as well as in test plots, and involving farmers in the selection process are other components of participatory plant breeding. In addition to providing well-adapted local varieties, participatory plant breeding has multiple other benefits. These include decreasing costs while educating and empowering all parties. It also facilitates uptake of new varieties (Najeeb et al., 2018).

Participatory plant breeding can also facilitate the optimization and use of suitable variety mixtures. Mixtures are a promising strategy to increase resilience, especially for self-pollinating or clonal crops. Different varieties planted in a single field can improve yield stability under variable biotic or abiotic stress conditions, or allow for continued adaptation to changing conditions (Cleveland et al., 2000; Murphy et al., 2005; Phillips & Wolfe, 2005). For example, East African farmers grow mixtures of many varieties of common bean that are resistant to different diseases at different sites. Some Andean farmers maintain a large variety of different potato cultivars via harvesting and planting bulk mixtures (Cleveland et al., 2000). Evolutionary plant breeding is another strategy that can provide genetically diverse and resilient crops for sustainable agriculture (Döring, Knapp, Kovacs, Murphy, & Wolfe, 2011; Murphy et al., 2005;

Phillips & Wolfe, 2005; Raggi et al., 2017). In this case breeders produce heterogeneous composite cross populations with high inherent genetic diversity, for example to biotic or abiotic stressors (Jackson, Kahler, Webster, & Allard, 1978). These populations are successively selected under low-input conditions in natural cropping systems, often within participatory plant breeding programs. Over time, breeder and/or farmer selection can produce heterogeneous populations or pure lines well-adapted to variable low-input cropping systems.

A final important consideration running through all of plant breeding is one of control, and thus power. Conventional and GM plant breeding currently encourage or require the yearly purchase of seeds by farmers. GM crops also have patent restrictions on research, seed saving, and use for breeding. Their development requires specialized knowledge, equipment, and reagents. These factors keep control in the hands of seed companies and large institutions. To support food and seed sovereignty, in addition to using participatory methods, sustainable plant breeders must prioritize varieties that facilitate farmer seed saving and adaptation. These should be unpatented and free from other restrictions, particularly on seed sharing, breeding, or research.

13.6 Conclusions: Obstacles and opportunities

While in theory it might someday be possible to create a GM crop that meets the broad requirements of sustainable agriculture, in practice this seems highly unlikely to ever happen (Kesavan & Swaminathan, 2018; Wickson et al., 2016). Nevertheless, despite their numerous technical, ecological, and social failings (e.g., Benbrook, 2018; Fischer, 2016; Wickson et al., 2016), GM crops are commercially successful, dominating the market for specific commodity crops in a number of countries. This success has been attributed to various factors. Farmer surveys suggest HT crops can save time and provide more spraying flexibility, and *Bt* crops are considered “insurance” to reduce risk. Research also suggests farmers often have limited seed options, and they often are locked into technological treadmills, in part due to a loss of knowledge about alternatives, or a belief that a technology is inevitable (Pechlaner, 2010; Stone & Flachs, 2018).

Ultimately, however, the commercial successes of GM crops are due to politics, rather than technical factors. Science and technology are not neutral (O'Brien, 1993). GM crops support conventional agriculture, which in turn supports a vast corporate agro-industrial complex (Lima, 2015). For economic and ideological reasons, the US government, nongovernmental organizations, universities, and academics work with agribusiness to promote the uptake of GM crops and technologies, tailoring public research, government regulation, and subsidies to promote their rapid acceptance and expansion, while suppressing unwelcome findings and locking out alternatives (Binimelis et al., 2009; Cáceres, 2015; Capellesso et al., 2016; Foscolo & Zimmerman, 2013; Harsh, 2014; Peekhaus, 2010; Pelletier, 2005, 2006; Robinson, Holland, Leloup, & Muilerman, 2013; Schnurr, 2013; Schnurr & Gore, 2015; Schreiner, 2009; Vanloqueren & Baret, 2009; Waltz, 2009). The mainstream media further support

these efforts by consistently portraying GM crops and technology as promising and technically successful (Barker, 2014; Stone, 2017).

In spite of these systemic biases, there are signs of change. Some commodity crop farmers in the United States have abandoned GM crops and substituted more sustainable regenerative practices (LaCanne & Lundgren, 2018). Some GM plant breeders have switched from GM to conventional and participatory plant breeding (Ceccarelli & Grando, 2019; Gilbert, 2016). Meanwhile, the acreage of land under organic production has increased (Paull, 2017). Numerous researchers from different disciplines have called for both agricultural practices and plant breeding to become more socially and ecologically sustainable and reject GM crops (Kesavan & Swaminathan, 2018; Kremen & Miles, 2012; McIntyre et al., 2009; van Bueren, Struik, van Eekeren, & Nuijten, 2018). These are all hopeful signs that the scientific and political momentum is building to end the transgenic treadmill and transition to the agroecological and regenerative practices needed to underpin a sustainable food system, one that can support healthy people on a healthy planet (Anderson & Rivera Ferre, 2020; Valenzuela, 2016).

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