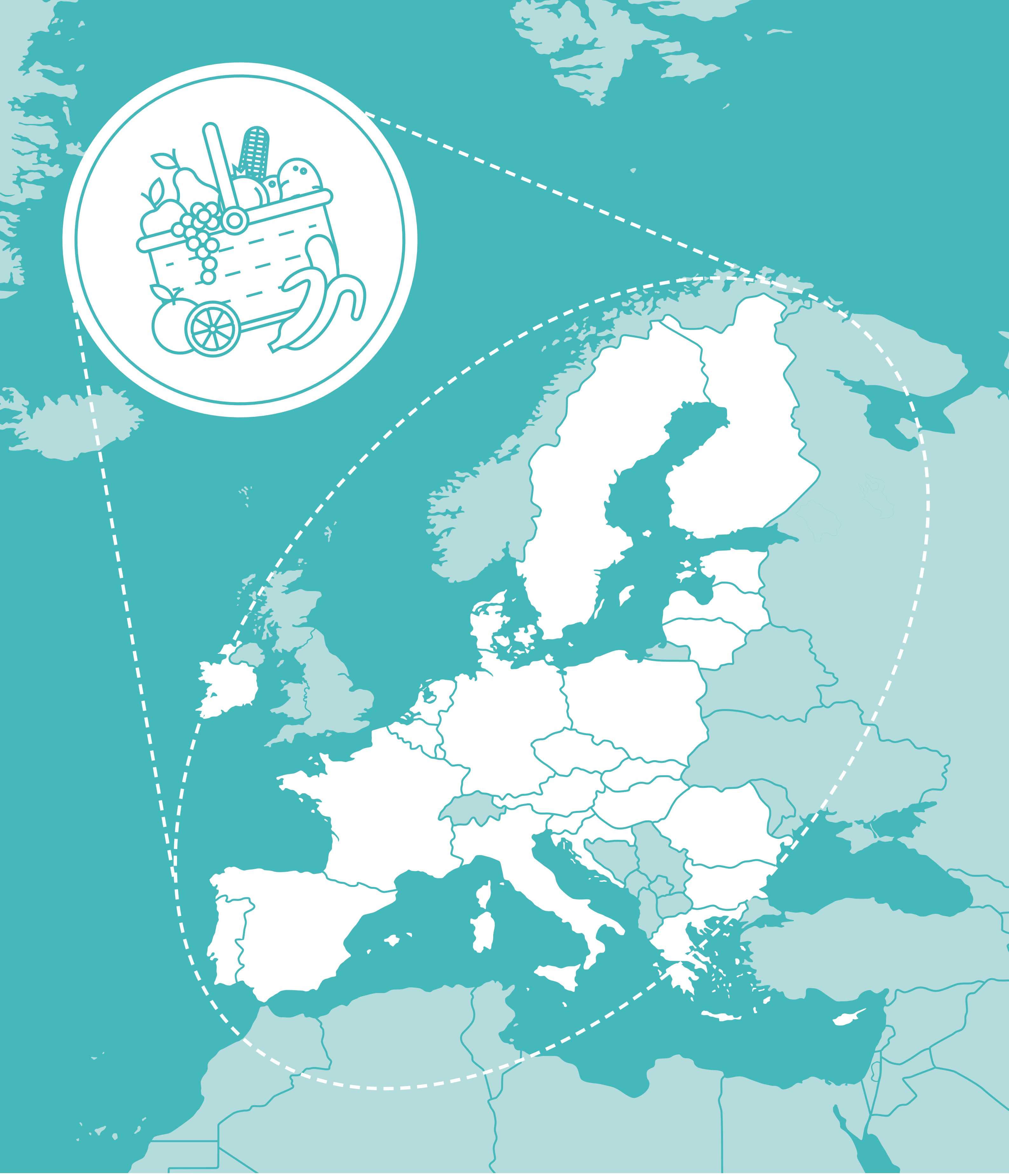

GENOME-EDITED CROPS
A EUROPEAN PERSPECTIVE

epp group
in the european parliament

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INTRODUCTION LETTER

This evidence-based study is inspired by the discussion about how to mitigate the impact of climate change on our agriculture, ensure food security and nutrition as well as support the competitiveness of European farmers.

Based on communication with different stakeholders, including consumers and farmers, I have discovered that information about new genomic techniques (NGTs) and their acceptance vary. Currently, we hear a strong voice of scientists, who clearly demonstrate how research has progressed. Scientific results offer acceptable, safe and effective breeding methods such as genome editing. This breeding method results in crop varieties necessary to ensure food security for people in the EU and beyond, while being environmentally friendly and meeting the requirements of good agricultural and environmental conditions. These new varieties would also be more resistant to drought and pests, which would enable the reduction in pesticides use.

The wide use of NGTs in the EU is not possible due to very strict EU legislation, which de facto blocks the introduction of the new varieties resulting from genome editing on the European market. If we want to change the current situation, we should introduce changes to the current regulatory framework. To do so, we need to facilitate communication on the topic of NGTs with citizens and various stakeholders. Our approach to this vital issue should be evidence-based and without ideological prejudices. This study, which was created by European experts in the field of new breeding techniques, is intended to serve this purpose. We aim to inform citizens and stakeholders that there are various tools in the breeders' toolbox and genome editing is one of them.

During the work on the legislation for plants produced by certain new genomic techniques, our aim is to set transparent procedures for assessment of new plant varieties obtained with genome editing, ensure fair conditions for the companies on the market, including SMEs, and to work towards biodiversity increase.

I would like to thank EU-SAGE for providing their expertise in this report and to all authors for their contributions. I am very proud of the Czech researchers who participate in the scientific discussions on genome editing as well as in this study. I hope that the study will be one of the steps on the way forward to the adoption of new EU NGTs legislation.

Michaela Šojdrová
Member of the European Parliament

M Šojdrová

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I. GLOBAL CHALLENGES SET THE SCENE

With a world population that is still continuing to grow, the demand for food and resources will also continue to grow worldwide.

Natural resources required for food and non-food biomass will however become more limited, and ecologically valuable natural landscapes contributing to biodiversity are lost at increasing pace. The climate crisis is upon us, and its impacts are getting more severe with each passing year.

Global actions to slow down climate change are promising but likely insufficient. More substantial investment in efforts to adapt to conditions like higher temperatures, longer periods of drought and more unpredictable rainfall are needed. Agriculture and food production will need to adapt to these changing conditions and innovations in breeding technology including the application of modern gene technology are among the factors that may help to address these challenges.

The ongoing Presidency of the Czech Republic of the EU Council provides an excellent opportunity to take advantage of such an important topic, the resolution of which would be of great benefit to the sustainability impact of EU agriculture and food.

2. THE ROLE OF GENE TECHNOLOGY AND NEW GENOMIC TECHNIQUES

Gene technology is playing an important role in today's society. This can be clearly seen in human medicine where it all started with the production of human insulin in the beginning of the 1980ties. Many other human medicines have followed.

Over the last years, oncology has been revolutionized by therapies, where patient's own immune cells are genetically modified and infused back into the body where they recognize and eliminate cancer cells. Today, a growing group of patients all around Europe receive such treatments and make full recovery. The recent vaccines against the SARS-CoV2 virus are also products of gene technology. In life sciences research, the role of gene technology is even more prominent and decades of gene technology-based research have led to vast amounts of knowledge on the basics of life and the underlying molecular mechanisms in health and disease. This in turn has spurred the development of novel diagnostics, vaccines and therapeutic products.

In contrast, despite the wide acceptance of gene technology in medicine, its role in agriculture and food production - especially in Europe – is much less prominent. Outside Europe millions of hectares of genetically modified (GM) crops are grown while in Europe the acreage is very limited. These GM crops are all based on technology developed in the 1980ties through which a piece of DNA is inserted into the genetic material of a plant. In recent years, gene technology has considerably advanced. New, more targeted technologies have been developed and these techniques are often referred to as 'novel genomic techniques' (NGTs). One particular type of technology is 'genome editing', which refers to techniques that can precisely introduce targeted changes within the existing genetic blueprint/ material of an organism. The term 'targeted mutagenesis' also refers to techniques that introduce such changes. In practice, it is the so-called 'CRISPR-Cas' technology that is used in the vast majority of cases to introduce targeted changes into the genome of organisms. This genome editing technology was introduced in 2012 and has dramatically increased the efficiency with which desired genetic changes can be introduced into crops. In October 2020, Jennifer Doudna and Emmanuele Charpentier were awarded the Nobel Prize in Chemistry for the development of the CRISPR-Cas genome editing tool. This document serves to explain the relevance of genome editing technology for agriculture and food production and to formulate recommendations for policy.

JENNIFER DOUDNA

EMMANUELE CHARPENTIER

3. FROM FIELD SELECTION TO GENOME EDITING

Agriculture begun about 10.000 years ago with people starting to sow seeds on plots of land. Over time, farmers turned to selection of seeds from best-performing plants, thereby starting a process leading to higher yields and favoring plants with desired properties.

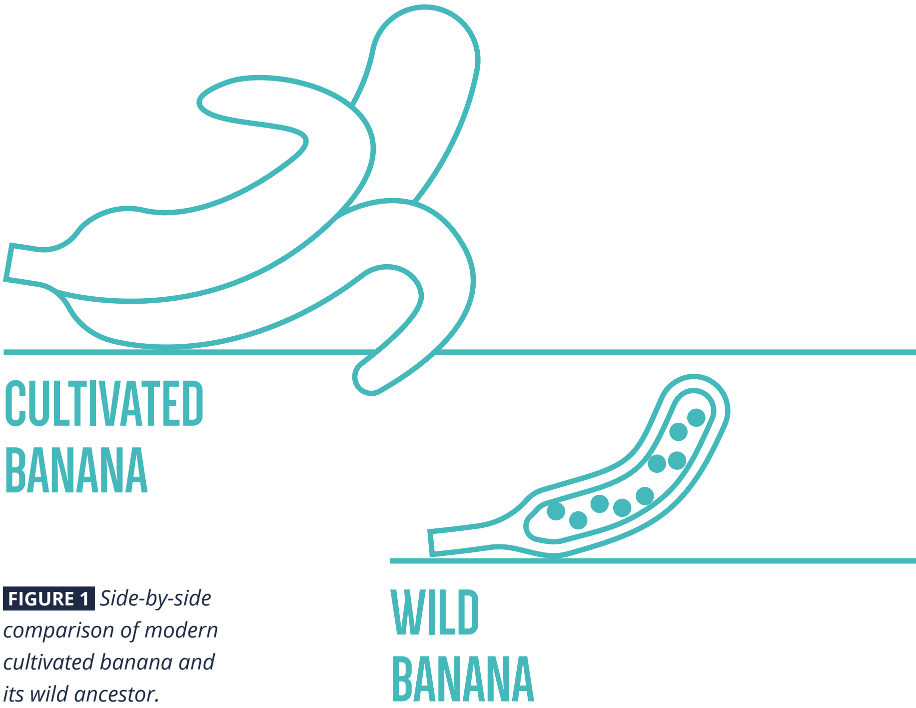


FIGURE 1 *Side-by-side comparison of modern cultivated banana and its wild ancestor.*

For thousands of years this was a slow process in which the crop plants as we know them today slowly emerged from wild plants. A good example can be seen in figure 1 below. This evolution of crop plants happened because of the gradual accumulation of spontaneous changes in their DNA. In later phases, farmers also started to cross plants with different, desired properties in the hope to combine them in the next generation plants.

It was the discovery of the laws of inheritance as proposed by Gregor Mendel in 1865 and 1866 that formed the basis for a breakthrough in plant breeding. This only materialized after the re-discovery of these laws of inheritance in 1900 by Hugo de Vries and Carl Correns. The genetic knowledge gathered by Mendel created a basic understanding of how hereditary properties are passed on from one generation to the next and this turned plant breeding into a science-based and professional activity.

During the course of the 20th century additional technological developments have followed allowing plant breeders to develop improved varieties. In the first half of the century the first hybrid varieties were produced, and embryo rescue and the technique to change the number of chromosome sets were developed. In 1953 James Watson and Francis Crick unraveled the double-helix structure of DNA, thereby also explaining how genetic material is replicated and passed on from one generation to the other without losing any information. In that same period and continuing during the 1960ties Norman Borlaug laid the foundation for the Green Revolution. It was the selection of short stem varieties of cereals combined with the use of synthetic fertilizer and other improvements of crop management that formed the basis for the Green Revolution and which led to significant increases in grain yield, thereby contributing to preventing food shortages. In 1970 Borlaug received the Nobel Peace Prize for his work.

JOHAN GREGOR MENDEL, “FATHER OF GENETICS”.

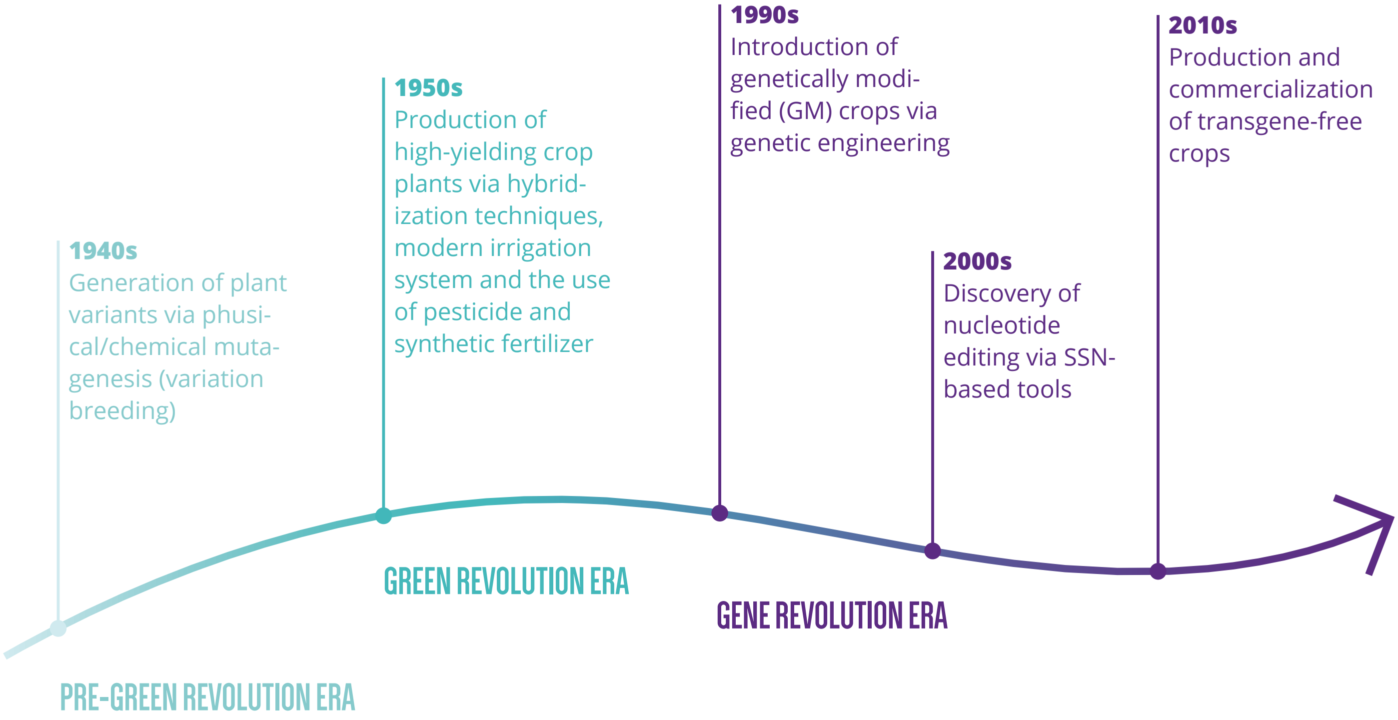


FIGURE 2 *The shift from the Green Revolution to the Gene Revolution era with an indication of important events*

Figure copied from Hamdan et al, Green revolution to Gene revolution: technological advances to feed the world, Plants, 2022

Also the techniques of mutation breeding and the ability to regenerate whole plants from in vitro plant tissue were developed. Mutation breeding makes use of radiation or certain chemicals to induce random changes in the plant genome. Among the induced random changes – also called mutations – there may be one or a few that result in a useful new property in the plant. Today, many food crops have properties that have been introduced through the application of mutagenic agents. The joint FAO/IAEA Mutant Variety Database (Mutant Variety Database - Home (iaea.org)) lists more than 3000 plant varieties that have been made using conventional random mutagenesis. Well-known examples are the durum wheat that is used to make bread and pasta, and pink grapefruit.

In the second half of the 20th century, as a result of growing genetic knowledge and the development of techniques such as marker-assisted breeding, DNA-sequencing and genetic modification, the Green Revolution has evolved into a ‘gene revolution’, indicating that breeding has evolved to become more and more based on genetic knowledge (figure 2). Marker-assisted breeding has made it possible for breeders to select plants with certain genetic properties without having to grow multiple plants and check each one for the presence of these properties.

The development of genetic modification of plants by Jeff Schell and Marc Van Montagu in the 1980ties led to the development of so-called transgenic crops; crops in which pieces of DNA that are foreign to the crop’s genetic material are introduced.

Taken together, all these developments have one thing in common – the outcome is about obtaining plants with improved properties that result from genomes in which small changes have taken place and/or different beneficial properties have been combined. Many of the food crops that are available on our market shelves today are hybrids, have an altered number of chromosome sets and/or have properties that have been introduced through the application of mutagenic agents.

EVOLUTION OF BARLEY, WHEAT AND OATS YIELDS OVER THE LAST SEVEN CENTURIES

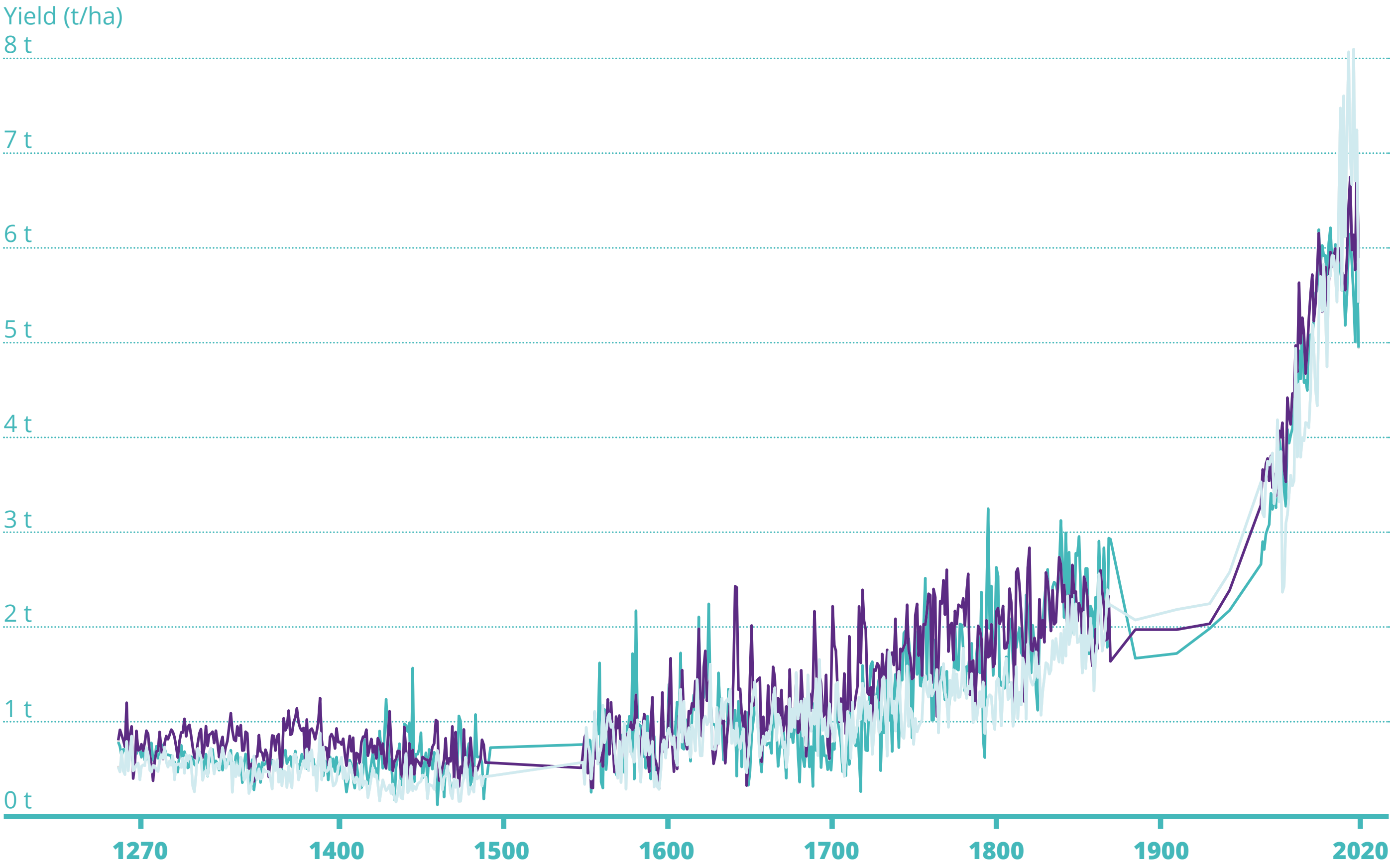


FIGURE 3 *Evolution of barley, wheat and oats yields over the last seven centuries*

Fouquet R. and Broadberry S., Seven Centuries of European Economic Growth and Decline, Journal of Economic Perspectives, 2015; FAO DATA

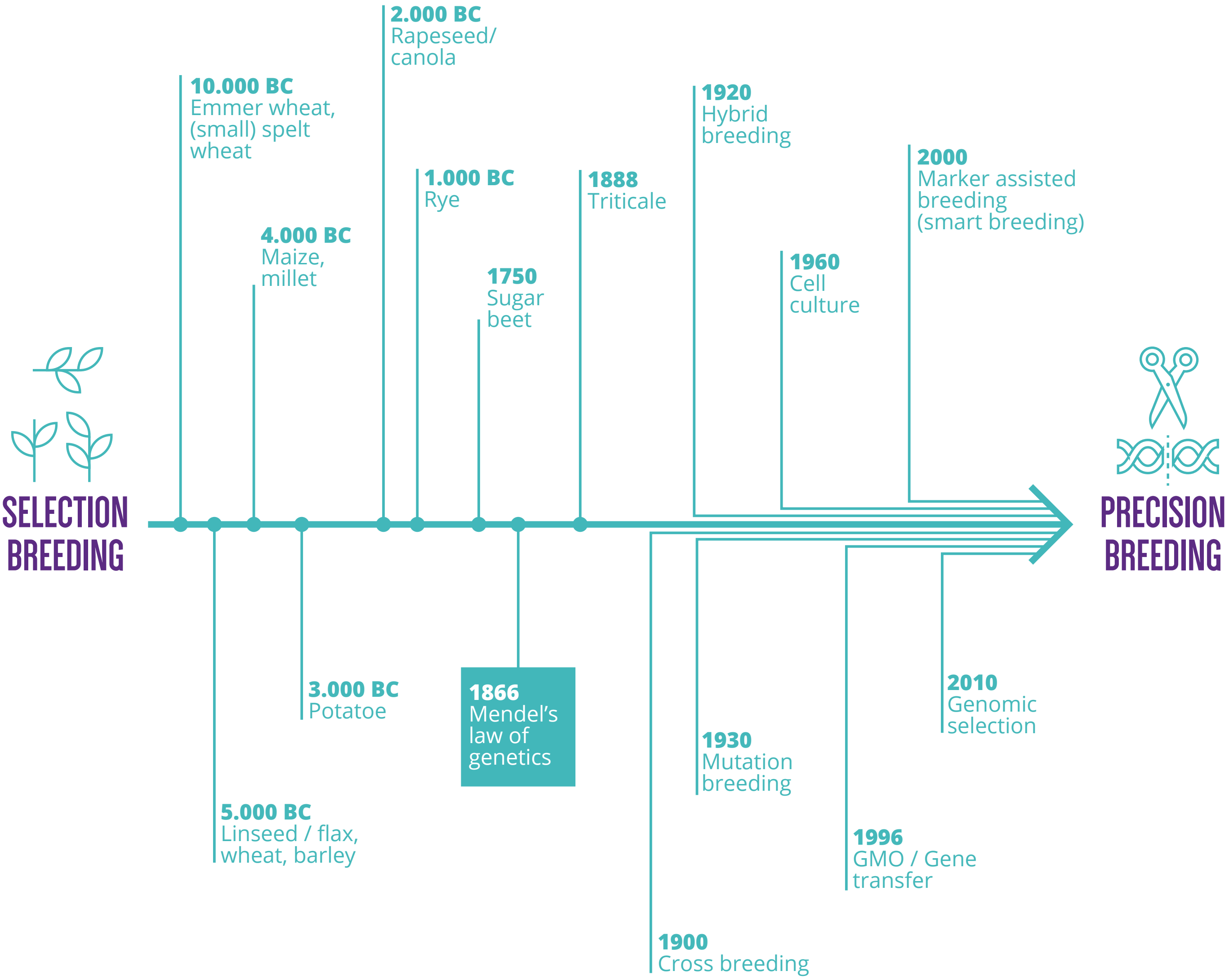
■ *Barley*
■ *Wheat*
■ *Oats*

The productivity of crops has dramatically increased in the 20th century (figure 3). It is estimated that around 66% of the yield increase in the past two decades is the result of plant breeding efforts.

Genome editing technology has now been added on top of all these developments. Overall, plant breeding has become more targeted and more precise. It is also for that reason that the latest developments in plant breeding are often referred to by the term ‘precision breeding’ (figure 4).

MILESTONES IN PLANT BREEDING

FIGURE 4 *The evolution of technologies in plant breeding*



4. GENOME EDITING TECHNOLOGY AND ITS APPLICATION

Genome editing is about the introduction of targeted changes within the existing genetic blueprint of an organism. There are different genome-editing technologies, including so-called TALENs, ZFN technology, Oligo-Directed Mutagenesis and CRISPR-Cas technology.

The CRISPR-Cas genome editing tool has been developed from a naturally occurring mechanism allowing bacteria to defend themselves against certain viruses. The scientific tool adapted from this system consists of two components that form a complex: The first one - a guide RNA molecule - functions like the ‘FIND’ function of a text processor: it searches through the genome of the organism until it has found the matching DNA sequence. It can be designed to find and match any DNA sequence. The second part of the tool is the Cas protein which acts as a molecular scissor that can cleave the DNA either halfway or completely. It cleaves the DNA only when the guide RNA has attached to its target sequence allowing for unmatched precision. Once the break of the DNA at the desired location has taken place, the natural DNA repair mechanism of the cell initiates its repair to stitch the DNA back together.

This repair has a very high fidelity to repair the DNA to its former state. But sometimes a small error occurs during the repair and the DNA is no longer 100% identical to the original. This is how a permanent small change to the DNA - also referred to as mutation - is introduced. Such a change can be the deletion of one or a few DNA letters, the addition of one or a few DNA letters or the alteration of one DNA letter into another DNA letter (table 1). One can also add a DNA template and introduce this together with the guide RNA and Cas protein. The DNA template will then direct the DNA repair and result in the introduction of a specific change as determined by the template. Such a DNA template can also be

TABLE 1 *The types of DNA changes that can be introduced using CRISPR-Cas*

THE TYPES OF DNA CHANGES THAT CAN BE INTRODUCED USING CRISPR-CAS
The deletion of one or a few DNA letters, or larger stretches of DNA
Point mutations (the alteration of a DNA letter into another DNA letter)
The addition of one or a few DNA letters
Rewrite a stretch of DNA
Replace an existing gene by another version of that same gene
Insert a larger piece of DNA (complete genes) at a desired location

used to introduce foreign genes and sequences into the genome of the crop species, leading to the formation of a transgenic crop. Additional variants of the CRISPR-Cas technology have been developed, allowing for precise editing of one DNA letter ('base-editing'), or re-writing pieces of DNA ('prime-editing').

The types of DNA changes that are introduced in this way are identical to the types of DNA changes that can spontaneously occur in nature or result from conventional breeding, unless the technology is used to introduce genes or sequences that are foreign to the genome/genetic material of the plant species. Many of such DNA changes have already occurred during plant breeding and have been selected to become present in cultivated varieties. The difference between what has happened during the history of plant breeding and what is happening now with genome editing, is that plant breeders now have the possibility to deliberately introduce targeted changes to the DNA and are no longer fully dependent on random genetic variation. Other advantages of CRISPR-Cas technology are that is now possible to edit different genes at the same time, and to edit different copies of the same gene at the same time.

CRISPR-Cas technology has an enormous potential in significantly shortening the development times of new plant varieties. Using conventional breeding it can take up to 20 years or more to develop a new variety (figure 5), whereas genome editing can speed up the new plant variety breeding process to only 2 to 7 years. CRISPR-Cas technology offers also new possibilities in plant species in which crossbreeding is not possible today, for instance because the species is sterile, such as banana.

The EU-SAGE database[1] lists more than 600 peer-reviewed research articles (October 2022) in which genome editing has been used to introduce market-oriented traits in over 60 different crops. There are examples of plants with improved food/feed quality, increased yield and growth, resistance against plant pests and diseases, resistance to abiotic stress such as drought, altered plant color and flavor, and more (table 2). From the EU-SAGE database it does not become apparent which crops will actually be developed to be marketed, it only indicates genome-edited plants that are described in scientific publications. But it does show the potential of the technology. The question is whether it will become possible to exploit that potential in the EU.

An important pre-condition for the application of CRISPR-Cas is that relevant genetic knowledge must be available about the role and function of specific genes and its variants, how they interact with other genes and the environment, and what the effect is of altering these genes. When such knowledge is not available, which may be the case for certain plant species, then it is not possible to apply genome editing in an efficient manner.

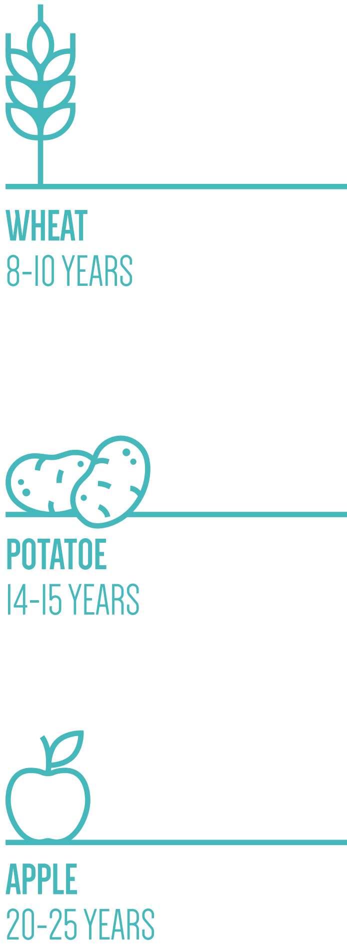


FIGURE 5 *Duration of conventional breeding technology to produce a new variety*

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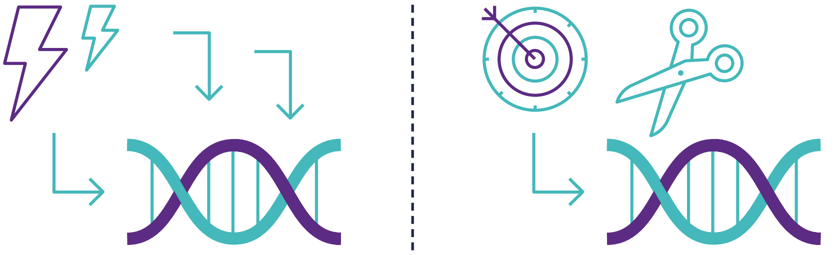
[1] › *www.eu-sage.eu/index.php/genome-search*

EXAMPLES OF GENOME-EDITED CROP PLANTS DESCRIBED IN SCIENTIFIC LITERATURE
Rice with **increased tolerance to salinity**
Vitamin-enriched (Beta-carotene) banana
Rice with **reduced unhealthy nutrient content**
Lettuce with **increased vitamin C content**
Tomato with **enhanced resistance to fungus** (Phytophthora)
Orange with **increased bacterial resistance**
Tomato with **increased health benefits** (gamma-butyric acid content)
Apple with **increased resistance to fungus** (fire blight)
Virus resistant cucumber
White strawberry
Drought tolerant wheat
Peanut with **improved diet composition** (fatty acid content)
Grapevine with **increased resistance** against fungus (powdery mildew)
Potato **free of (toxic) unhealthy glycoalkaloids**
Oilseed rape with **less yield loss** (increased resistance pod shattering)
Maize with **improved starch composition**

TABLE 2 *Examples of genome-edited crop plants described in scientific literature*



CONVENTIONAL MUTAGENESIS

- Random change in genome
- Number of genes affected: hundreds

GENOME EDITING – CRISPR-CAS

- Targeted change in genome
- Number of genes affected: 1 or more, as designed

FIGURE 6 *Comparison of the genetic changes introduced through conventional mutagenesis and CRISPR-Cas*

A comparison of CRISPR-Cas technology with conventional random mutagenesis which uses radiation or chemicals to introduce genetic changes or mutations illustrates how much more precise this technology is. In conventional mutagenesis many hundreds of random mutations are induced, some of which may result in a desired property. Genome editing ensures that only the desired mutation(s) is (are) induced (figure 6).

There are worries regarding occurrence of so-called off-target changes: these are unintended genetic changes at other locations in the genetic material of a plant. With current genome editing technology the chances of such off-target changes occurring are very low. To avoid that plants with undesired changes are introduced on the market, edited plants must be genetically characterized, and only the plants containing the desired changes must be selected. Furthermore, breeding by itself inevitably creates a mixing of the genetic blueprints of the parents, causing much more extensive changes than the small genetic changes introduced by genome editing.

Genome editing is a technology that can complement existing breeding methods in the development of improved plant varieties. It is an additional tool in the plant breeders' toolbox and depending on the challenge that plant breeders aim to address they will choose the breeding method or combination of breeding methods that suits their aims best. Conventional breeding will remain extremely important to develop varieties that are adapted to specific regions and specific climatic conditions.

5. THE ROLE OF PLANT BREEDING INNOVATION TO ADDRESS CHALLENGES IN EUROPEAN AGRICULTURE AND FOOD PRODUCTION

EU agriculture and food production faces important challenges; challenges that have become even more apparent in Europe during 2022 as a result of extreme drought and warfare. Climate adaptation, food security and improving the sustainability of agriculture and food production are at the top of the EU policy agenda.

One of the objectives is to reduce the use of chemical plant protection products by 50 % by 2030. However, there is no clear roadmap on how to replace these compounds, or introduce other ways to maintain high yields and avoid contaminations by harmful organisms that may produce toxins. Another challenge is to achieve zero nitrogen and phosphorus pollution from fertilizers by reducing nutrient losses by at least 50 %. This target should lead to a 20 % reduction in fertilizer use by 2030. Similar to the case of plant protection products, there is no clear plan on how to maintain high yields with reduced supplies of nutrients. According to USDA[2] the proposed input reductions would affect EU farmers by reducing their agricultural production by 7 - 12 % and diminish their competitiveness in both domestic and export markets.

A variety of measures may be considered to secure environmentally sustainable production of food in sufficient quantity and quality under the conditions envisaged by the Green Deal. One of the key elements will be the cultivation of new varieties adapted to climate change, resistant to diseases and pests and with higher efficacy of nutrient use.

It was shown that plant breeding has contributed to about 66% of the yield increases during the past two decades, thereby providing a crucial contribution to the ability to feed the current world population of 7.7 billion people. Similarly, plant breeding can provide important contributions to climate adaptation of crops, to food security and improve sustainability of agriculture and food production. The opportunity offered by genome editing, is that those contributions can be achieved in a much more directed and faster way. This will not apply to all crops and for all types of desired traits, but in many occasions genome editing may prove to be an efficient tool to achieve a specific breeding goal.

2 › Beckman et. al., Economic and Food Security Impacts of Agricultural Input Reduction Under the European Union Green Deal's Farm to Fork and Biodiversity Strategies, EB-30, U.S. Department of Agriculture, Economic Research Service, 2020

CROP	INTRODUCED PROPERTY	POTENTIAL BENEFICIAL EFFECT IN THE CONTEXT OF EU AGRICULTURAL CHALLENGES
Grapevine	Increased resistance to fungus *(Erysiphe necator)*, causing powdery mildew	Reduced dependency on the use of chemical or organic fungicides
Wheat	Resistance against fungus powdery mildew	Avoidance of the use of chemical or organic fungicides to combat powdery mildew
Potato	Resistance to potato virus X	Reduction of yield loss following potato virus X infection
Citrus fruit	Resistance against bacteria *(Xanthomonas citri)* causing citrus canker	Reduction of yield loss
Wheat	Drought tolerance	Reduction of yield loss under dry conditions
Tomato	Enhanced tolerance to heat stress	Better performance under heat stress
Maize	Drought tolerance	Reduction of yield loss under dry conditions
Rice	Enhanced salinity tolerance	Enhanced yield under salinity stress conditions
Oilseed rape	Improved pod shattering resistance	Reduced seed loss during harvest, thereby increasing yields and reducing volunteer plants
Maize	Increased total kernel number or kernel weight	Higher yield per unit of land
Lettuce	Enhanced photosynthesis and decreased leaf angles for improved plant architecture and high yields	Higher yield per unit of land
Tomato	More fruits and bigger fruits	Higher yield per unit of land
Barley	Increase in plant height, tiller number, grain protein content and yield	Higher yield per unit of land and increased quality
Pennycress	Domestication of wild pennycress by the targeted modification of six genes resulting in a winter crop with a better nutritional profile, higher oil content, reduced seed dormancy and more consistent germination	Cover of fallow croplands in winter, thereby reducing nutrient leaching, soil erosion and avoidance of the use of herbicides before sowing summer crops. The crop itself can be used as animal feed.

TABLE 3 *Examples of genome-edited crops and their potential benefits in the context of EU agricultural challenges*

A VERY DIVERSE EU AGRICULTURAL LANDSCAPE

The agricultural landscape in Europe is very diverse for different reasons. There are different climatic zones and different types of landscape that determine the type of agriculture that can be performed. The agriculture in different regions in the EU has also evolved in different ways. This makes that there are large differences in the size and the character of farms and the level of technology that is being applied. The crops that are being grown are also very diverse. From very large crops to very small crops for niche markets. Europe generally does not know the extremely large farms that are present in some regions in North and South America. Each of the different farmers in different European regions, focusing on different crops, will also be confronted with typical problems. Drought is a problem in southern parts of Europe, but due to climate change affecting also other areas. Insect pests are expanding their habitats, and specific crops will have their own typical diseases.

POTENTIAL BENEFITS FROM DIFFERENT COUNTRY PERSPECTIVES

Genome editing may help to address a number of those crop and region specific challenges and scientists in different countries are involved in projects to address them. In the Czech Republic for instance, scientists together with hop breeders aims to identify genes for dwarfism in hops and use genome editing to create dwarf hop plants from elite cultivars. Such dwarf hop plants would have benefits in improving the efficiency of hop cultivation.

Another example is the cultivation of root chicory in the Netherlands, Belgium and the north of France for the production of inulin. Inulin is a dietary fiber that is used as a food ingredient and which promotes gut health. In the CHIC project genome editing is used to generate root chicory that has an improved production and/or produces more bio-active terpenes which have medicinal properties (www.chicproject.eu).

In Sweden, scientists have used genome editing to develop potato varieties that produces only one type of starch. The benefit of such potatoes is that for certain non-food applications it is no longer necessary to exploit a chemical process for the removal of the undesired form of the starch.

Genome editing can also help preserve local, traditional varieties. This can be illustrated with an example of wine production with traditional varieties in Italy. Wine industry today suffers from a sustainability problem because it uses significant amounts of chemicals to safeguard yield. Replacing current varieties like Sangiovese with newer, more disease resistant varieties may be difficult for cultural reasons. Obtaining a disease-resistant Sangiovese using conventional breeding is not really possible without losing important characteristics of this traditional variety. However, with genome editing it is possible to introduce resistance against fungal disease while maintaining the traditional Sangiovese variety characteristics.

6. REGULATORY CHALLENGES IN EUROPE FOR DIFFERENT TYPES OF GENOME-EDITED PLANTS

> In the EU, crops in which genetic changes have been introduced by means of conventional random mutagenesis are GMOs but are exempted from the provisions of the EU GMO legislation.

Crops in which targeted genetic changes have been introduced using CRISPR-Cas are GMOs that are not exempted from the provisions of the EU GMO legislation (figure 7). As a consequence, plants in which the same genetic change has been introduced - in one case by means of conventional random mutagenesis, and in the other case by means of CRISPR-Cas - , are treated differently in the EU GMO legislation.

The EU GMO regulatory framework presents one of the most stringent regulatory frameworks in the world. Only large multinational companies are able to afford the cost and complexity triggered by the regulatory requirements. It is difficult to get a GM crop authorized in the EU for import and processing into food and feed. It is almost impossible to get a GM crop authorized for cultivation in the EU. There is one GM crop that is authorized to be cultivated in the EU (MON810 insect-resistant maize). Later attempts to get other GM crops authorized for cultivation in the EU have been withdrawn.

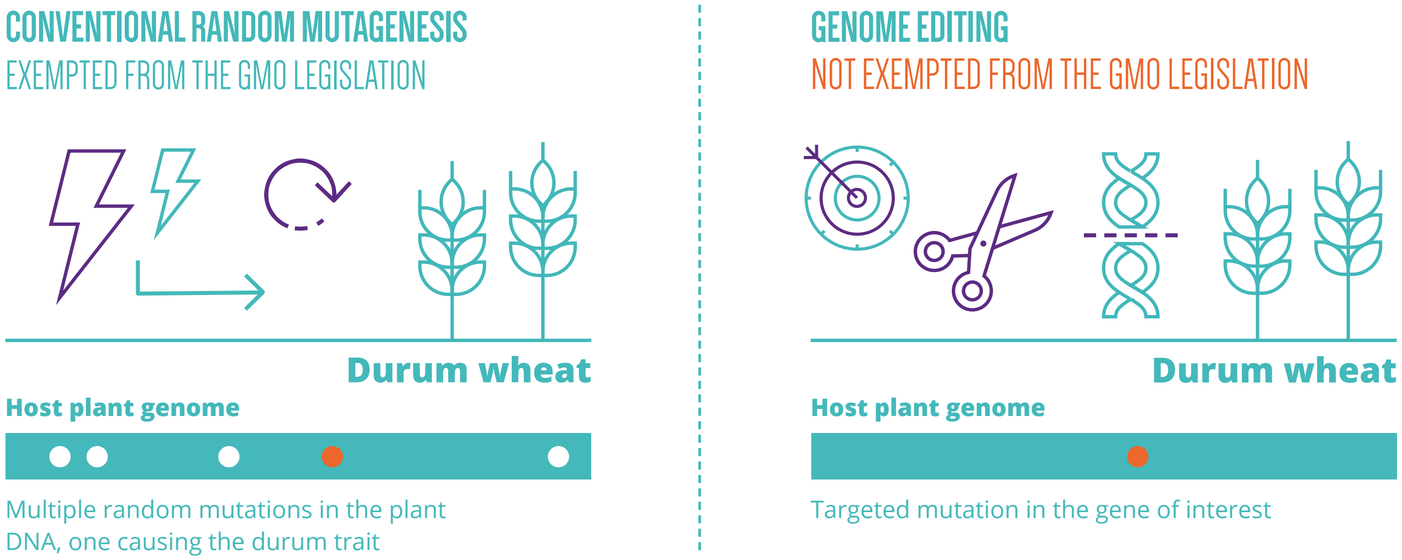


FIGURE 7 *The regulatory status of randomly mutated plants compared to that of genome-edited plants*

Whether it is possible to get a permit for a field trial with a GM crop differs from country to country in the EU. In countries like Belgium, Sweden, Spain and also The Netherlands field trials are possible, while in countries like Germany, France or Austria such field trials are currently not realistic. The number of field trials currently conducted in the EU is small[3].

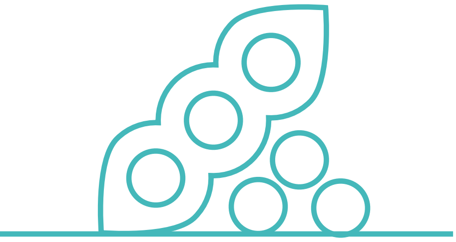
Genome-edited crops have potential to provide positive contributions in the context of current agricultural challenges. But regulating them as GMOs will render obtaining an authorization for cultivation in the EU as good as impossible. In that scenario it will be very unlikely that genome-edited crops will be able to realize their potential in the EU.

There is a need to re-think the regulatory approach for genome-edited crops, especially for those types of genome-edited crops in which targeted changes have been introduced that can also occur naturally and/or result from conventional breeding activities. CRISPR-Cas technology is a very versatile breeding technology that can also be used by public breeding institutions and SMEs and can be used in small market share crops for which genetic knowledge exists about relevant genetic changes and their effects.

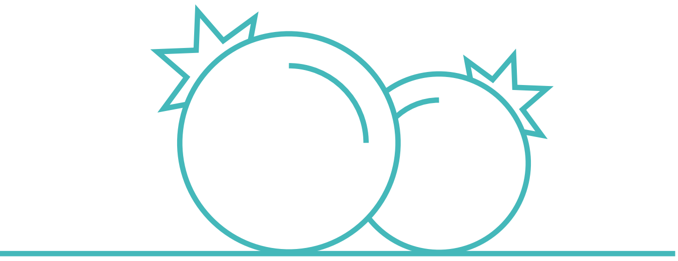
In its Study on the status of new genomic techniques under Union law, the European Commission states that the current EU GMO regulatory framework is not fit-for-purpose for regulating certain types of modified crops. In the autumn of 2021 the European Commission initiated a process to develop new legislation for crops resulting from targeted mutagenesis and cisgenesis[4]. In the autumn of 2021 an inception impact assessment was published, and in the spring and summer of 2022 stakeholder surveys and stakeholder interviews were held to gather views and information that will form the basis of an impact assessment. The European Commission intends to publish a regulatory proposal for crops resulting from targeted mutagenesis and cisgenesis before the summer of 2023.

AN INTERNATIONAL PERSPECTIVE

New genomic techniques, and especially CRISPR-Cas technology, has led to policy discussions in many regions and countries in the world. A number of South-American countries (Argentina, Brazil) were among the first to adapt a regulatory approach in which they exempt genome-edited crops from the scope of their GMO legislation on the condition that the introduced changes could also have occurred naturally or result from conventional breeding activities. Other countries have followed to introduce a regulatory regime that is similarly favorable to specific categories of genome-edited crops (figure 9 and table 5). This has also led to the first genome-edited crops being introduced onto the market. Genome-edited high-oleic oilseed soybean is on the US market and genome-edited tomato with increased levels of gamma-aminobutyric acid (GABA) is on the Japanese market. GABA is a compound that can help lower blood pressure (figure 8).



HIGH-OLEIC SOYBEANS IN THE US



HIGH GAMMA-AMINOBUTYRIC ACID (GABA) TOMATOES IN JAPAN

FIGURE 8 *The two genome-edited crops currently on the market: high-oleic soybeans in the US and high gamma-aminobutyric acid (GABA) tomatoes in Japan*

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[3] *https://webgate.ec.europa.eu/fip/GMO_Registers/GMO_Part_B_Plants.php*

[4] *Cisgenesis is not really a breeding technique, but refers to organisms in which genes that exist within the organism's gene pool have been introduced into the genome of that organism*

REGULATORY APPROACHES TOWARDS GENOME-EDITED CROPS

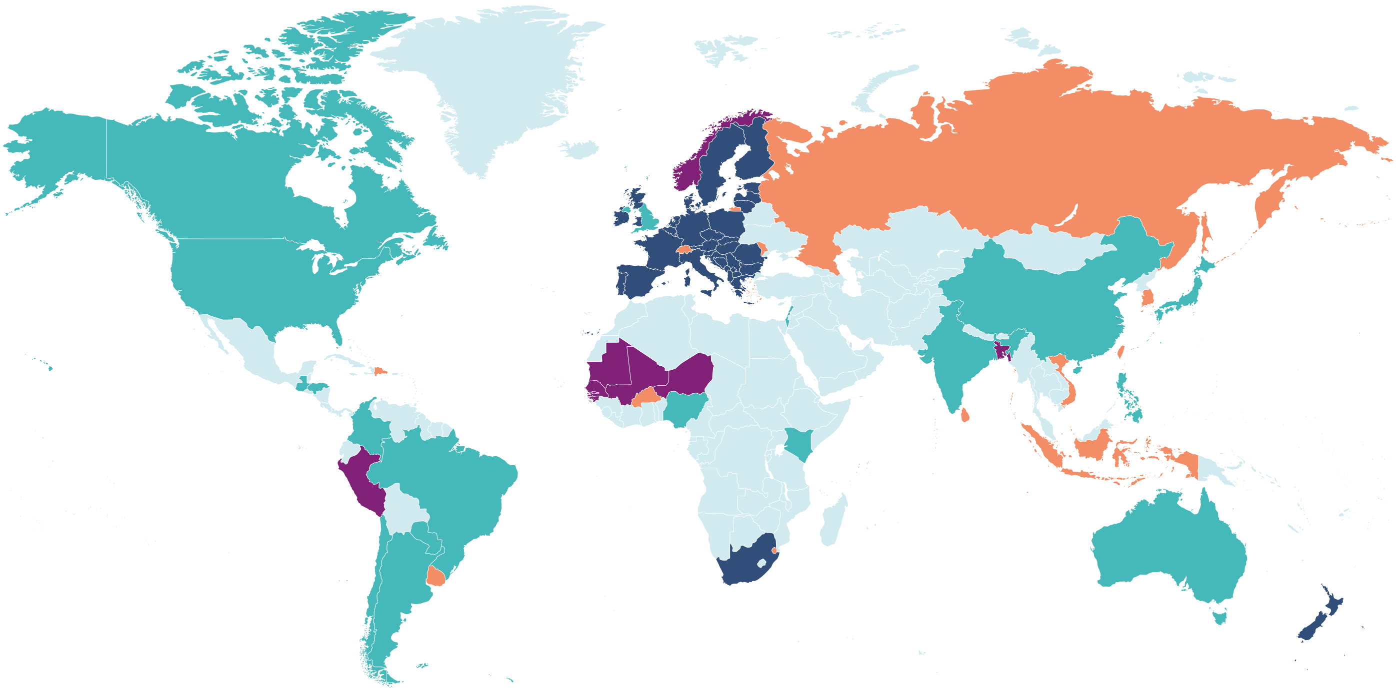


FIGURE 9 *Regulatory approaches towards genome-edited crops.*

Figure 9 is copied with permission from the publication Sprink et al, Genome editing around the globe: an update on policies and perceptions, Plant Physiology, 2022.

- 🟩 *Legislation open towards genome editing*
- 🟧 *Open legislation or positive statement being prepared*
- 🟪 *Discussion ongoing with no decision yet*
- 🟦 *Strict GMO regulation for genome-edited products*
- ⬜ *No discussion or no information available*

COUNTRY	REGULATORY APPROACH TO SPECIFIC CATEGORIES OF GENOME-EDITED PLANTS
Argentina	Non-GMO classification of organisms that do not have a ‘new combination of genetic material’, meaning that if a genetic change could have occurred naturally or result from conventional breeding they are not treated as GMOs. A verification process is place for the non-GMO classification.
Australia	Organisms in which a genetic alteration is the result of genome-editing without using a DNA template to direct the alteration, are not a GMO.
Brazil	Non-GMO classification of organisms that do not have a ‘new combination of genetic material’, meaning that if a genetic change could have occurred naturally or result from conventional breeding they are not treated as GMOs. A verification process is in place for the non-GMO classification.
Canada	Canada does not have a GMO legislation, but legislation for plants with novel traits. The application of plant breeding methods including genome editing does not lead to a plant with a novel trait if the genetic alteration does not alter proteins to become more similar to known allergens or toxins, does not increase levels of known endogenous toxins or allergens, does not have an impact on key nutritional composition and/or metabolism, does not intentionally change the food use of the plant, and does not result in the presence of foreign DNA.
China	Genome-edited plants in which no foreign genetic material has been introduced would be treated differently than transgenic plants. Genome-edited plants for agricultural use would be divided into four different categories with ascending information requirements.
England	Plants that could have resulted from traditional processes can be released into the environment on the condition that the release is notified to the authorities. A permit is not required. A voluntary verification process exists to have confirmed that the plants could have resulted from traditional processes.
India	Genome-edited plants in which no foreign genetic material has been introduced is proposed to be treated differently than transgenic plants. Depending on the genetic alteration introduced in the plant there would be a tiered assessment that would determine which information would need to be provided.
Japan	Organisms in which a genetic alteration is the result of genome-editing without using a DNA template to direct the alteration, are not a GMO. Organisms in which a DNA template has been used to direct the genetic alteration are not a GMO if the altered DNA sequence is naturally occurring.
USA	The following plants are exempt from the US Plant Pest regulations: › Plants with a change resulting from cellular repair of a targeted DNA break in the absence of an externally provided repair template › Plants with a single base pair substitution › Plants in which genes are introduced known to occur in the plant’s gene pool

TABLE 4 *Regulatory approaches to genome-edited crops in other countries in the world*

REGULATORY SCENARIOS AND THEIR CONSEQUENCES

Different regulatory approaches will have different effects and consequences. Below a qualitative estimate is given of the likely consequences of the implementation of different regulatory scenarios for crops resulting from targeted mutagenesis and cisgenesis in the EU.

SCENARIO 1

The status quo scenario

In this scenario the current regulatory policy is maintained in which organisms with targeted genetic changes are GMOs that are subject to the provisions of the EU GMO legislation.

› Only large corporations will be able to market genome-edited crops in the EU. Public breeding institutions and SMEs will not be able to enter the market.
› It will be very difficult to get a genome-edited crop authorized for cultivation in the EU.
› The high regulatory costs and complexity will prevent that genome-edited crops will be developed and marketed for smaller market share crops and for niche markets.
› It maintains a situation in which crops with the same genetic change, but made with different technologies, are treated differently.
› There will be an indirect negative effect on the introduction of genome-edited crops in countries outside the EU where there is a risk that this crop ends up in products that are exported to the EU.
› The non-supportive regulatory climate for genome-edited crops will have a negative impact on plant research in the EU as their possibilities decrease to translate scientific findings in which genome-edited crops play a role, into benefit for society.
› It will be difficult to enforce the GMO legislation as there are no technical means to determine with which breeding technology a small change to the gene of a plant was made. There is a traceability problem.
› The difference between the regulatory approach in the EU and the regulatory approach in other countries is likely to lead to issues in international trade.

SCENARIO 2

A lighter risk assessment framework for genome-edited crops

In this scenario crops resulting from targeted mutagenesis and cisgenesis would be subject to a less elaborate pre-market risk assessment than is currently applied for GM crops.

› Depending on the actual data requirements, in this scenario there will be more possibilities for a wider group of companies to develop and market genome-edited crops in the EU.
› What will the voting behavior be of the EU member states in such an adapted regulatory framework?
› It maintains a situation in which crops with the same genetic change, but made with different technologies, are treated differently.
› It will be difficult to enforce this legislation as there are no technical means to determine with which breeding technology a small genetic change to the gene of a plant was made. There is a traceability problem.
› Differences remain between such a regulatory approach in the EU and the regulatory approach in other countries, which is likely to lead to issues in international trade.

SCENARIO 3

A regulatory framework that treats certain genome-edited crops as conventional

In this scenario, crops in which targeted mutations have been introduced that could also occur naturally or result from conventional breeding are treated in the same way as conventional crops, meaning that there is no authorization procedure that requires an (elaborate) pre-market risk assessment. There may be a notification or verification procedure that needs to be followed to have officially confirmed that the crop is indeed falling into this category. The EU general food safety legislation and the EU environmental liability legislation will apply, and in some cases the genome-edited crop may qualify as a novel food, thereby triggering a pre-market novel food safety assessment.

› It will be much easier for public breeding institutions and SMEs to develop and market genome-edited crops in which genetic changes have been introduced that could also occur naturally or result from conventional breeding. It is more likely that also genome-edited varieties of smaller market share crops are developed and placed on the market.
› Crops with the same genetic change, but made with different technologies, are treated equally.
› This regulatory approach is more in line with the regulatory approach in other countries in the world, which may prevent that issues in international trade arise.
› Farmers and consumers have the same access to such genome-edited crops and products as in other regions and countries in the world, thereby avoiding competitive disadvantages.

Food, feed and environmental safety are very important principles in the EU. In scenario 3 the responsibility for the food, feed and environmental safety lies more with the developer of the crop, similar to the situation for conventional crops. No explicit government pre-market verification of the safety is performed. The question is whether this would lead to unacceptable safety risks. Plant breeders have elaborate experience with the development of new varieties, and during the development process they also collect significant amount of data about the performance and behavior of the plants. Many ten-thousands new conventional varieties have been developed and placed on the market, which all genetically differ from prior varieties. The balance of that experience is positive with less than a handful known exceptions where the new variety had an undesirable health effect. These new varieties were taken of the market.

7. PERSPECTIVES, THE WAY FORWARD AND RECOMMENDATIONS

The way agriculture evolves is intrinsically linked to progress in science and technology. Outcomes of scientific research are translated to the dinner table, involving different steps. The following elements are important to enable this translation:

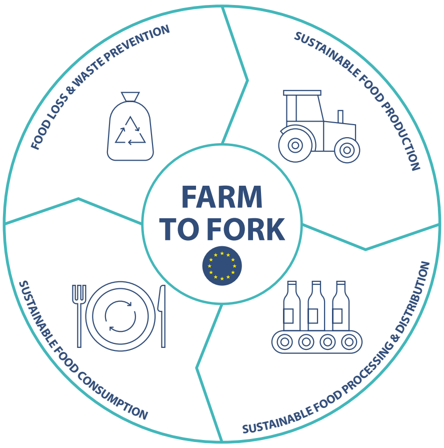
- Knowledge, expertise and a willingness to invest in the development of a product or technology
- an innovation-friendly climate that enables the transition from research to the production system
- a proportionate regulatory framework that allows innovations to arrive on the market without unnecessary constraints
- consumer acceptance and uptake of the innovations by the agri-food systems.

Technological improvements in agriculture over the last decades have led to increasing productivity, achieving high quality food standards and maintaining reasonable prices of food. Today, in European agriculture, genetic innovations in plants reach the market only with great difficulties mostly due to regulatory constraints.

Agriculture is sometimes portrayed in a rather romanticized manner and the perception of how our agricultural system functions may not be realistic. The agricultural system is a man-made system that has had a profound effect on the natural ecosystem. It follows the laws of artificial selection. The agricultural environment changes faster than a natural environment would and cultivated varieties must adapt to new growth conditions and new threats. This is one of the reasons why plant varieties are continuously improved.

Today the European Green Deal and the ‘Farm to Fork’ Strategy form the context that will shape the direction in which plant breeding needs to evolve. The EU needs to find ways to reduce dependency on pesticides and fertilizers and reverse biodiversity loss while at the same time provide society with sufficient, nutritious, sustainable and affordable food. Innovation will have to play a role in the transition in different ways. Genome editing is one of the innovations available which can help address some of the challenges that plant breeders are currently facing in their efforts to improve plant varieties in directions that help achieve important sustainability goals.

With the use of genome editing, plant breeding sets an additional step in becoming ever more knowledge based. Compared to more conventional approaches genome editing is associated with less uncertainties, which contributes to safety. It is not the use of a particular technology that will determine whether a certain crop is safe. Safety is predominantly determined by the final characteristics of the plant and the way it is grown in practice. Sometimes it is perceived that genome editing would enable plant breeders to develop crops that can go directly from the R&D facility to the dinner table. This is not the case: genome editing is only part of the breeding cycle and plant breeders still need to go to the



field and thoroughly analyze the characteristics of the plants over multiple years and on several locations to come to a variety that can be placed on the market. And as said earlier, genome editing is only one of the tools in the plant breeders' toolbox and depending on the challenge that they aim to address they will choose the breeding method, or combination of breeding methods, that suits their aims best.

Scientific literature shows that genome editing is able to achieve a wide variety of breeding goals and that it can achieve them in a more directed and faster manner. It also shows that characteristics can be introduced that are relevant in the context of the objectives of the Green Deal, the "Farm to Fork" Strategy and the United Nation's Sustainable Development Goals. But to be able to deliver on its potential, more is necessary. Without farmers, food industry, retailers and consumers being receptive to the use of genome editing in agriculture and food, plant breeders will be hesitant to invest in NGTs. A wider understanding of the evolution and role of innovation and technology in plant breeding can form a foundation upon which further communication can build. Transparency about the use of NGTs is also seen as an important factor to build trust. Surveys in Norway and Sweden have shown that citizens are open to the use of genome editing technology and that the level of support depends on the purposes for which the technology is used. Health related characteristics and traits that can help reduce the use of pesticides are well received.

The legal situation in the EU is a dominant factor in the current inability of genome editing to deliver on its potential in the EU. The study of the European Commission concluded that the current GMO framework is no longer fit-for-purpose for certain types of modified crops and has prompted the Commission to come forward with a legal proposal for crops resulting from targeted mutagenesis and cisgenesis before the summer of 2023. It goes without saying that the content of that legal proposal will determine the future of genome editing and how it will be able to contribute to more sustainability in the agricultural system.

Recommendations to be considered for the way forward:

1. Create a wider understanding of the role of innovation and technology in the development of the wide array of crops and foods that consumers have at their disposal.

2. Create transparency about the use of NGTs and find ways to inform the consumer in a manner that creates understanding about what the technology is used for.

3. Engage with countries outside of the EU to learn from their regulatory approaches and the effect these approaches have on the development of new varieties and products.

4. Remove the current disproportionate regulatory thresholds for the marketing of certain types of genome-edited plants in a way that would enable plant breeders to develop and market genome-edited crops that can contribute to achieving the goals of the Green Deal, the Farm-to-Fork Strategy and the UN Sustainability Goals.

5. In the development of a proportionate regulatory framework for NGTs, strive for harmonized approaches, including the perspective of food safety.

6. Take a regulatory approach that also allows SMEs to benefit from the use and application of genome editing and that strengthens the diversity of the EU agricultural system.

ANNEX: A COUNTRY PERSPECTIVE ON GENOME EDITING – THE CZECH REPUBLIC

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THE CHARACTERISTICS OF CZECH AGRICULTURE

Agriculture has a long tradition in Czech Republic and is well advanced. Recently released crop varieties and cultivars are grown and cutting-edge technologies are used in plant cultivation, animal husbandry and product processing. Although the agriculture contributes only about 2.13% to the Czech Gross National Product, it plays a critical role in food security. The high quality of Czech agricultural products is evidenced by the results of inspections by supervisory authorities. The structure of Czech agriculture stems from historical contexts that determine the current size of agricultural enterprises. Around 29,000 agricultural entities are registered in the Czech Republic, and the average size of the farm is 121 ha, which is significantly above the average of 28 ha of the entire EU.

Internal organization of the farms underwent extensive changes after political changes in the 1990s. The biggest of them is a shift from animal husbandry to crop production, which accounts for more than 60% of the total output. A smaller part of agricultural production is allocated for energy production. As a consequence, a limited spectrum of crops is grown on large areas and intensive use of land negatively affects biodiversity. The cultivation of a few crops, shortage of farm manure and use of heavy machinery contributes to degeneration of agricultural soils, which lack enough organic matter. There is an urgent need to increase the content of organic matter in the soils to revive microbial life and improve their biological, chemical and physical properties. The poor state of agricultural soils also compromises the ability to retain water in the landscape.

CHALLENGES IN CZECH PLANT BREEDING

In the Czech Republic breeders are aware of the needs of the Czech farmers, who like farmers in other EU member states are facing pressure to use less pesticides. In principle, the most economic and sustainable solution is to cultivate disease and pest resistant crops. This is why a majority of plans to use genome editing in the Czech Republic focuses on resistance genes. Other targets that have been identified as interesting are improving the quality of crops and editing of genes and/or genetic pathways that control the production of storage compounds and chemical composition of plant tissues, fruit tissues and seeds. Regarding adaptation to climate change, Czech scientists state that it may be useful to alter the time of flowering and improve frost tolerance to avoid freeze damage in fruit trees and decrease the negative effect of drought periods on yields. Also prolonged shelf life, changed mode of plant reproduction and modified plant morphology are identified as interesting breeding targets.

Hop is a typical and important Czech crop. Hop is one of the main ingredients of beer and plays an important role in providing certain aromas in the beer. There is a collaborative project involving the Institute of Experimental Botany of the Czech Academy of Sciences, Institute of Biophysics of the Czech Academy of Sciences and hop breeders aims to identify genes for dwarfism in hops and use genome editing to create dwarf hop plants from elite cultivars. Such dwarf hop plants would have benefits in improving the efficiency of hop cultivation.

FIELD RESEARCH

In the Czech Republic it is difficult to obtain a permit for a field trial with a GM crop. In the past various GM crops have been in field trials in the Czech Republic (namely soybean, sugar beet, corn, potatoes, barley, pea, flax, plum and tobacco). However, at present barley is the only GM crop with a pending approval from the Ministry of the Environment of the Czech Republic for a field trial. The main obstacles mentioned are a complicated bureaucracy, a need for duplicities in equipment for harvesting and storage and mainly problems to find partners in the food industry for subsequent GM crop processing.

CROP	TRAIT	QUALITY / RESISTANCE	GENE KNOWN
Wheat	Wheat dwarf virus (WDV)	R	N/A
	Barley yellow dwarf virus (BYDV)	R	Yes
Barley	Barley yellow dwarf virus (BYDV)	R	Yes
Clover	Fusariosis (F. oxysporum, etc.)	R	N/A
	Powdery mildew (Erysiphe trifolii)	R	N/A
	Clover rot (Sclerotinia trifoliorum)	R	N/A
	Virosis (AMV, BYMV, RCVMV)	R	N/A
	Clover anthracnose (Kabatiella caulivora)	R	N/A
	Organic matter digestibility (OMD)	Q	N/A
	Phytoestrogen content	Q	Yes
Grasses	Rust (Puccinia graminis, P. coronata)	R	N/A
Pea	Powdery mildew (Erysiphe pisi)	R	N/A
	Pea seed-borne mosaic virus (PSbMV)	R	N/A
Fruit trees	Columnar growth (not only for apples)	Q	Yes
	Early flowering of small trees	Q	Yes
	Self-fertility of apple trees	Q	Yes
	Anthocyanins in the pulp	Q	Yes
	Slow oxidation of the pulp	Q	Yes
	Plum pox virus (PPV)	R	Yes
	Fire blight (Erwinia amylovora)	R	Yes
	Powdery mildew (Podosphaera leucotricha, P. clandestina)	R	Yes
	Apple scab (Venturia inaequalis)	R	N/A
	Modulating of flowering (delaying)	Q	N/A
	Bud frost tolerance	Q	N/A
	Preventing the softening of the fruits	Q	N/A
	Parthenocarpy and seedlessness	Q	N/A

TABLE A1 *Examples of traits identified by Czech breeders as targets for genome editing*

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