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COMMISSION ON GENETIC RESOURCES FOR FOOD AND AGRICULTURE

Item 9 of the Provisional Agenda
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RECENT DEVELOPMENTS IN BIOTECHNOLOGIES RELEVANT TO THE CHARACTERIZATION, SUSTAINABLE USE AND CONSERVATION OF GENETIC RESOURCES FOR FOOD AND AGRICULTURE

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I.   INTRODUCTION

1.   In 2011 and 2015, the Commission on Genetic Resources for Food and Agriculture (Commission) reviewed the latest developments in biotechnologies and their implications for the conservation and sustainable use of genetic resources for food and agriculture (GRFA).[1] The Commission's Multi-Year Programme of Work (MYPOW) foresees, for the Commission's forthcoming Eighteenth Regular Session, another "review of the work on biotechnologies for the conservation and sustainable use of genetic resources for food and agriculture."[2]

2.   At its Thirteenth Regular Session, the Commission considered an overview of the then current status of biotechnology applications for the characterization, conservation and utilization of GRFA, as well as of the comparative advantages that biotechnologies can provide over conventional technologies. At its Fifteenth Regular Session, the Commission considered the document *Application and integration of biotechnologies for the conservation and sustainable use of genetic resources for food and agriculture*.[3]

3.   The present document provides an update on recent developments in biotechnologies relevant to the characterization, sustainable use and conservation of GRFA. Because of the wide array of different "technological applications that uses biological systems, living organisms, or derivatives thereof, to make or modify products or processes for specific use,"[4] FAO usually uses the term "biotechnologies" rather than "biotechnology". Research and development of biotechnologies combine disciplines such as genetics, molecular biology, biochemistry, embryology and cell biology.

II.   INTRODUCTION RECENT DEVELOPMENTS IN BIOTECHNOLOGIES RELEVANT TO THE CHARACTERIZATION, SUSTAINABLE USE AND CONSERVATION OF GENETIC RESOURCES FOR FOOD AND AGRICULTURE

Across sectors

4.   Over the past 15 years, there have been rapid and ever-increasing advances in science and technology, institutional and human capacities and infrastructure in the field of gene sequencing and in the associated bioinformatics (the application of information technology and computer science to the field of molecular biology) and high-performance computing. Genomic data have allowed the accumulation of massive amounts of information related to molecular biology and helped to improve understanding of biological processes.

5.   Genomics includes the study of gene networks and gene-related metabolism, and – along with other "omics" – helps to illustrate the functions of DNA and other heritable and non-heritable molecules. The term "omics" encompasses genomics, the study DNA, with subfields including structural genomics, functional genomics and epigenomics, and fields that focus on the analysis of other classes of molecules such as RNA (transcriptomics), proteins (proteomics), lipids (lipidomics), carbohydrates (glycomics) and metabolites (metabolomics).

6.   Technology developments have significantly increased the throughput of DNA and RNA sequencing and reduced the costs and time involved in generating massive amounts of sequence data, a lot of which are now publicly available. This has enabled the establishment of high-throughput next-generation-sequencing- (NGS)-based genotyping platforms used to develop comprehensive polymorphism datasets, including single nucleotide polymorphisms (SNPs), Indels (insertion and deletion variants), structural variations and genomic rearrangement (Nguyen *et al*., 2019). These and similar resources have in turn permitted the accelerated mapping of quantitative trait loci (QTL) and gene discovery in crops and livestock, including through genome sequence assemblies, resequencing of thousands of individual plants and animals, and − taking advantage of genome-wide methodologies

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[1] CGRFA-13/11/3; CGRFA-15/15/7.
[2] CGRFA-17/19/Report, *Appendix F, Annex 1*.
[3] CGRFA-15/15/7.
[4] Convention on Biological Diversity: definition of biotechnology.

− the development of haplotype maps for several agricultural species,[5] high-density genetic maps and a range of marker genotyping platforms and the identification of markers associated with agronomic traits (Varshney *et al*., 2019).With regard to food and agriculture, benefits have been realized through biological similarity and genetic synteny with humans and model species. In general, investment in the study of these latter species has driven development of scientific knowledge and bioinformatic resources that can be applied to GRFA.

7.   Taken together, genomics and bioinformatics are increasing the efficiency of the characterization of germplasm and the development of improved livestock breeds and crop varieties through marker-aided selection (MAS), marker-assisted recurrent selection (MARS) and, more recently, genome-wide or genomic selection and genomics-assisted breeding (GAB). Genomic selection, applied across sectors to commercially bred species with large phenotype databases, has reduced generation intervals and increased genetic gains. It also increases the risk of inbreeding if genetic markers are not used to control inbreeding levels.

8.   Genetic modification, or transgenesis, approaches are targeting particular genes or parts of the genome. Gene-editing through clustered regularly interspaced short palindromic repeats (CRISPR/CAS 9) has provided breeders with another potent tool, the impact of which can be increased by the application of reproductive technologies (e.g. cloning). A challenge for genetic engineering is to achieve stable transformation and produce individuals with modified gene structure; off-target alterations in the genome that may lead to unanticipated consequences are possible.

9.   The application of genomic tools depends heavily on the availability of a wide range of both genomic and phenotypic data. The ease with which sufficiently large sets of phenotypic data can be collected determines the prediction accuracy of the algorithms for genomic breeding values. In some cases, phenotyping has become more costly than genotyping. Usually, only large populations of commercially important genetic resources benefit fully from genomic selection. Large amounts of training data are needed for most applications. For instance, implementation of genomic selection in small livestock populations is very challenging, as the limited number of sires with large numbers of daughters and progeny tests restricts prediction accuracy (Jenko *et al*., 2017).

10.   The greater availability of molecular genetic and genomic data has given rise to the fields of bioinformatics and computational biology. Both deal with the collection, classification, storage and analysis of biochemical and biological information (e.g. DNA, RNA and amino-acid sequences) using computers and integrating and relating these data with each other and other types of data (e.g. agronomic traits, phenotypes and geographic information), especially as applied to molecular genetics and genomics.

11.   The distinction between the two fields is somewhat vague, and there is no consensus in this regard. For example, the thesaurus[6] of the National Cancer Institute of the United States of America considers the two terms to be synonyms. The difference lies perhaps in the perception of the relative importance of biological questions or objectives on the one hand and computational questions or objectives on the other in research and development. Applications in these fields require powerful computers and infrastructure for storing large quantities of data.

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[5] Cattle: http://www.bovinegenome.org; Goat: http://www.goatadaptmap.org; Horse: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5530493/; Pig: Megens *et al*., 2010 and https://comparativegenomics.illinois.edu/publications/abstract/porcine-hapmap-projects-genome-wide-analysis-pig-wild-boar-and-suiforme; Sheep: http://www.sheephapmap.org; Cattle, Bovine HapMap Consortium. 2009.
[6] "Bioinformatics (Code C17964); Preferred Name: Bioinformatics. Definition: Bioinformatics derives knowledge from computer analysis of biological data. These can consist of the information stored in the genetic code, but also experimental results from various sources, patient statistics, and scientific literature. Research in bioinformatics includes method development for storage, retrieval, and analysis of the data. Bioinformatics is a rapidly developing branch of biology and is highly interdisciplinary, using techniques and concepts from informatics, statistics, mathematics, chemistry, biochemistry, physics, and linguistics. It has many practical applications in different areas of biology and medicine. (M. Nilges and Jens P. Linge, Unite de Bio-informatique Structurale, Institut Pasteur, Paris). Synonyms & Abbreviations: Bioinformatics, Computational Biology" (https://ncithesaurus.nci.nih.gov/ncitbrowser/pages/home.jsf).

12.   An era of increasing digitization of information and rapid development of technologies to mine and integrate big and heterogeneous data has seen the emergence of biodiversity informatics, a discipline related to data science and bioinformatics that applies information technology methods to the collection, analysis and interpretation of digital information on living organisms, including on taxonomy and nomenclature, sequencing and other molecular data, genotypes/phenotypes and geo-localization of specimens, samples stored in gene banks, and internet databases and scientific literature.[7] In the context of food and agriculture, biodiversity information is the subset of such information that relates to micro-organism, plant and animal species that provide food and non-food agricultural products and to species associated with production systems, including beneficial organisms (e.g. symbiotic microbes, pollinators and biocontrol agents) and pests (e.g. pathogens, invasive plants and insect pests).[8] Several international initiatives are compiling global lists of species, for example the Catalogue of Life (CoL, 1.9 million species),[7] the Global Biodiversity Information Facility (GBIF, 1.0 million species),[8] the National Center for Biotechnology Information taxonomy database (NCBI, 487 000 species),[8] the Encyclopedia of Life (EoL, 1.9 million species)[9] and the Integrated Taxonomic Information System (ITIS, 856 000 species).[10] In addition, there are many specialized databases focusing on particular species and taxa (e.g. 178 databases listed in CoL), including those of importance to food and agriculture (International Network of Food Data Systems).[11]

13.   There is currently, however, no central point of access to integrated information on species of importance to food and agriculture for use in characterization, monitoring, conservation or breeding, i.e. no comprehensive list of species linked to experimental and molecular data, genotypes and phenotypes, records of specimens in the field and in genebanks, information on usage for food and agriculture, nutritional values, scientific literature and external databases. Challenges with regard to the creation of such integrated information resources may include 1) documenting all available relevant data on species important for food and agriculture, 2) collecting big data in a variety of formats and languages and 3) integrating data and offering analytical and visualization tools to non-experts for specific applications related to the characterization, use and conservation of biodiversity.

14.   The development of bioinformatics has depended on, and mirrors, technological development in biotechnology and information technology and the declining costs of information technology infrastructure. Bioinformatics importance for human health and well-being has fostered the establishment of public institutions, databases and other resources for bioinformatics and computational biology,[12] and these are available for use for species other than human and other purposes. In addition, the principles of open source and open access have been widely put into practice, allowing scientists around the world to freely obtain, utilize and modify much of the software, data, information, tools and platforms, including for exchanging and presenting novel research findings.

15.   The pace of the development of enabling policy regimes has lagged behind that of the science and technology that propel genomic innovations. For instance, in cases where genome editing results in expressive genetic modification, there is no agreement as to whether or not genome-edited organisms should be considered genetically modified organisms (GMOs) or as to whether, if they are considered GMOs, their release for human consumption and/or into the environment would be regulated by the Cartagena Protocol on Biosafety to the Convention on Biological Diversity. Developed countries have been taking decisions on the subject. For instance, the United States of America has decided that genome-edited crops "could otherwise have been developed through traditional breeding techniques," and therefore will not regulate them (Waltz, 2016a,b; USDA, 2018). In contrast, it regards gene-edited animals as akin to "drugs", and they will thus be subject to a

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[7] https://www.catalogueoflife.org

[8] https://www.gbif.org; https://www.ncbi.nlm.nih.gov/taxonomy

[9] https://eol.org

[10] https://www.itis.gov

[11] http://www.fao.org/infoods/infoods/food-biodiversity/en/

[12] National Center for Biotechnology Information of the United States of America (https://www.ncbi.nlm.nih.gov/); European Bioinformatics Institute (https://www.ebi.ac.uk).

substantially stricter level of regulation.[13] At the opposite end of the spectrum, New Zealand subjects the products of genome editing to the same regulations as GMOs (Fritsche, 2018). A recent ruling of the apex court of the European Union entails treating genome-edited organisms in the same way as GMOs (Callaway, 2018). However, regulation is lacking for the majority of developing countries.

16.   In parallel to the fast development of "omics", many so-called "low technologies" continue to be relevant. For example, the use of tissue culture, with or without genetic engineering, is developing exponentially. In terms of costs and infrastructure, tissue culture in fundamental research in agriculture and forestry is still an expensive technology that requires trained personnel and the use of modern equipment (especially in maintaining tissue-culture collections worldwide).

17.   The following paragraphs give some insight into sector-specific applications of biotechnologies and bioinformatics for the characterization, sustainable use and conservation of GRFA.

Animal genetic resources for food and agriculture

18.   "Traditional" reproductive biotechnologies such as artificial insemination, embryo transfer and *in vitro* fertilization continue to be used extensively, especially in developed countries and in major species and internationally transboundary breeds. Combining reproductive and genomic biotechnologies creates major synergies. Development and adaptation of these technologies for use in less common species and local breeds continues, but with less investment and thus at a slower pace.

19.   The application of biotechnologies, particularly genomic technologies, has continued to expand in line with trends that have been ongoing for years, or even more rapidly. Improvements in chemistry and bioinformatic methods have facilitated higher throughput and higher coverage, and the assembly of longer strands of contiguous DNA. For example, reference genomes for livestock species have been continually refined as the costs of DNA sequencing have fallen and technological development has allowed the assay of longer and longer strands of DNA and for errors made in earlier references to be corrected.

20.   Genomics has facilitated improvements to the molecular characterization of breeds in nearly all production systems and has contributed to the identification of genomic regions associated with both production traits and adaptive traits such as heat tolerance and disease resistance. Genome-wide association studies have been used to identify the variations responsible for numerous genetic defects and other traits with simple forms of inheritance.

21.   In some livestock populations, particularly in industrialized countries and in commercially important species, breeds and market chains, genomic selection has largely replaced the progeny test and other traditional approaches used in selection for quantitative traits. Selection within the Holstein breed of dairy cattle has been completely revolutionized. The possibility of accurately selecting bulls before their daughters have started lactating has decreased the average generation interval for males from approximately seven years to about two and a half years. Advances in reproductive technologies have complemented those in genomics to reduce this interval in females from about four years to about two and a half years. Genetic response has essentially doubled as a result of these innovations. Alas, the shortened generation intervals have also increased the annual rate at which losses in genetic variation due to selection occur.

22.   The impacts of biotechnologies on livestock production have been less profound in developing countries and for less common species and breeds, especially those kept in low-input/extensive production systems. The costs and availability of phenotypic data have become greater obstacles to the application of genomics than the cost of genomic technologies themselves. Accepting that full-scale genomic selection is currently unrealistic in countries that do not have established performance and pedigree recording systems, work has been done on the use of genomics to quantify the breedwise

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[13] https://www.fda.gov/animal-veterinary/biotechnology-products-cvm-animals-and-animal-food/animals-intentional-genomic-alterations; https://www.fda.gov/media/135115/download

composition of animals that have resulted from multiple generations of indiscriminate cross-breeding and then determine the optimal multibreed genotype for the production environment.

23.   In addition to applications in selection for sustainable use and in trait characterization, the decreased cost of genotyping has also created the opportunity to use genomics in animal genetic resources conservation. For *in vivo* populations, the use of genomic relationships rather than, or in addition to, pedigrees improves the precision of approaches such as optimal contributions selection that aim to balance response to selection and maintenance of genetic diversity. Genomics also provides opportunities that are not directly available through the use of pedigrees to maintain rare alleles. Genotyping also allows the management of cryoconservation to be improved by comparing the genotypes of animals with stored material to those of animals in live populations, followed by targeted collection of under-represented diversity. Application of these approaches has only begun, however.

24.   Proudfoot *et al*. (2020) note that "while selective breeding has been hugely successful at enhancing some production traits, the rate of progress is often slow and is limited to variants that exist within the breeding population. Genome editing provides the potential to move traits between breeds, in a single generation, with no impact on existing productivity, or to develop *de novo* phenotypes that tackle intractable issues such as disease."

25.   Various approaches such as the use of CRISPR to modify DNA sequencing have made gene editing of animal genetic resources relatively straightforward. These procedures, coupled with reproductive biotechnologies, including cloning, have allowed the production of numerous animals with altered alleles at the genes responsible for the simple inheritance of traits such as the absence of horns, the presence of a sleek hair coat (associated with heat tolerance) and resistance to deadly coronavirus in pigs (Lee *et al*., 2020).

26.   Gene editing has also been demonstrated as a potential tool in the process of genetic improvement and/or conservation. Inactivation of a single gene can render "host" animals sterile (male animals in most cases), allowing for the transplantation of cryoconserved primordial germ cells from a "donor" animal (Ciccarellia *et al*., 2020). Host animals of low genetic potential or from common breeds can thus be used to disseminate the genetics of superior contemporaries or propagate rare donor breeds. To date, no national authority has approved any genetically engineered terrestrial animals for use in the production of human food.

27.   The sky-rocketing availability of data from livestock genomics projects has triggered huge requirements for bioinformatics tools and capacities in the fields of database management, data exchange and analysis, and interpretation of various kinds of data (sequence, amino-acid and protein, phenotype and environment) (Singh *et al*., 2018). Beyond the challenges involved in developing accurate tools for the analysis of heterogenic data, linkages between digital resources and the accessibility of such resources have been reported as major challenges (Bruford *et al*., 2015). The development of participatory approaches, combined with mobile technology, potentially enables robust data collection. Most developments have primarily benefited widespread breeds raised in intensive systems. Developing bioinformatic tools that could support livestock keepers in more extensive systems in the management and selection of their breeds is a priority.

Aquatic genetic resources for food and agriculture

28.   In August 2019, FAO published the first report on *The State of the World's Aquatic Genetic Resources for Food and Agriculture* (FAO, 2019a), which provides new insight into the state of use of biotechnologies in aquatic genetic resources management. This report is primarily based on 92 country reports and five thematic background studies, including a study on genome-based biotechnologies in aquaculture (FAO, 2019b).

29.   Molecular tools are regularly used to characterize genetic resources, especially in research and development, but there remains a paucity of information on aquatic genetic resources, including those developed using biotechnologies, particularly below species level.

30.   Approximately 45 percent of cultured species reported by countries are farmed as wild types, and it is estimated that only around ten percent of global aquaculture production results from the systematic application of well-managed selective-breeding programmes. Such selection programmes,

with pedigreed populations, are essential precursors for the application of more advanced biotechnologies such as genomic selection. Application of biotechnologies such as selective breeding is generally concentrated in higher-value species (e.g. salmon and shrimp) produced in the developed world. The uptake of biotechnologies is relatively slow, especially in the developing world, where the majority of aquaculture production occurs.

31.   Genetic markers − mainly microsatellites or, increasingly, SNPs − are being used for pedigree assignment within breeding programmes, often improving their selection efficiency. There are a few examples of MAS based on QTL being used in commercial breeding programmes, for example for resistance to bacterial cold water disease in rainbow trout (*Oncorhynchus mykiss*) (Liu *et al.*, 2018). Genomic selection is now starting to be applied in a small number of breeding programmes, again mainly in salmonids and shrimp (Houston *et al.*, 2020).

32.   The considerable effort put into research on the production of transgenic fish in the 1990s has yielded few commercial benefits, due principally to regulatory constraints to their production for food. However, following an extended review and approvals process, a fast-growing transgenic Atlantic salmon was approved for commercial production in the United States of America and Canada in 2016 (Wargelius, 2019). It is the first, and so far only, transgenic animal that has been approved for human consumption; it has been marketed in Canada, with 4.5 tonnes of fillets sold in 2017 (Conley, 2018), and was planned to be on the market in the United States of America in late 2020 (The Fish Site, 2020). Expansion of production into a number of other countries is planned (ibid.). Research is ongoing in other sectors, including on the production of transgenic seaweeds and microalgae, often for non-food usage such a microalgae for biofuels.

33.   Research on gene editing is advancing; a number of gene-edited aquatic organisms have been produced, and it is evident that this technology has significant potential for application in aquaculture (Gratacap *et al.*, 2019). It is likely that commercial application will be constrained by regulations, particularly in jurisdictions that class gene-edited products as GMOs. However, in jurisdictions that exempt gene-edited products from genetic modification regulations, as has occurred for a gene-edited tilapia in Argentina (Fishfarmingexpert, 2018), the pathway to commercial adoption may be much quicker than for the aforementioned genetically modified salmon. However, overall, investment in the development of GMOs, which so far have had little impact on aquaculture production, distracts and takes attention and resources away from the need to accelerate the application of more traditional biotechnologies, particularly to develop well-managed selective-breeding programmes, which in turn could underpin the application of many other biotechnologies such as MAS and genomic selection.

34.   In addition to the application of biotechnologies to the development of improved farmed types for aquaculture, biotechnologies are routinely used for managing the health and biosecurity of aquatic organisms, for example in disease diagnostics, typically using polymerase chain reaction (PCR)-based tests, and in vaccine development.

35.   While the majority of biotechnology applications in aquatic genetic resources are in species used in aquaculture, there are some related to capture fisheries, including in the study of population genetics and in stock assessment. Examples include the application of large-scale genotyping for close-kin mark-recapture to estimate stock abundance in some high-value species such as tuna (Bravington *et al*., 2016) and the use of SNP markers in the definition of subpopulations (Weist *et al*., 2019).

Forest genetic resources

36.   The application of biotechnologies in the forest sector has continued to progress along a somewhat different path from that being followed in the other agricultural sectors. This is due to the fact that forest trees differ from crops and farm animals in some ways. First, forest trees are highly heterozygous and long-lived species, with late sexual maturity and long generation cycles. Second, like aquatic genetic resources, forest trees are largely undomesticated; in the case of species that are included in tree breeding programmes, the aim is typically population-level improvement rather than development of new varieties (with a few exceptions).

37.   Most of the global forest area (93 percent) consists of naturally regenerating forests (FAO, 2020). For these forests, molecular markers and genomics remain the most widely applied biotechnological tools for quantifying genetic variation within and among tree species and their populations and for better understanding the biology of trees and the genetic basis of their adaptation mechanisms. Studies with molecular markers have focused on an increasing number of tropical tree species in addition to temperate and boreal tree species. These studies have generated a wealth of information, not only on the geographical distribution of present-day genetic diversity across different populations of tree species, or across species' entire distribution ranges, but also on their evolution. Similarly, scientific advances and decreasing sequencing costs have led to increasing use of genomic approaches in tropical tree species. These efforts have increased knowledge about forest trees for both management and conservation purposes.

38.   A broader range of biotechnologies are used in the establishment of planted forests and to advance tree breeding. The use of micropropagation has maintained its dominant role in large-scale production of clonal planting stock in several economically important tree species, including acacias, eucalypts, pines and teak. The backbone of micropropagating forest trees has long been tissue cultures derived from samples of buds or shoots, but investments in somatic embryogenesis have increased considerably as it offers much higher multiplication rates than *in vitro* cuttings and greater possibilities for genetic modification. Therefore, the most advanced tree breeding programmes supporting large-scale industrial tree plantations have been the first to adopt somatic embryogenesis for micropropagating planting stock.

39.   The advent of MAS raised expectations that it would accelerate forest tree breeding, but progress has been slower than expected. Efforts to link quantitative traits in forest trees with molecular markers have revealed a large number of QTL with inconsistent performance across different environments and genetic backgrounds. Results from genome-wide association mapping (GWAS) have also been modest, as individual associations between markers and traits account only for very small proportions of the genetic variation. This has led to a paradigm shift in forest tree breeding, and efforts are now moving away from the mapping of marker-trait associations to the capture of the whole-genome effects, assisted by DNA markers. This genomic selection is a form of MAS in which a large number of DNA markers are used so that all QTL are linked with at least one marker. This approach has become feasible thanks to easy and cost-effective genotyping, and it has yielded promising first results with forest trees. Genomic selection has thus revived expectations that the breeding of forest trees will be enhanced and that long breeding cycles will be shortened.

40.   During the past few years, research using genetic modification technology − mostly gene knock-out, knock-in and similar approaches dealing with single gene or gene family modifications − has further increased understanding of tree biology, in particularly growth-related processes and biochemical pathways. It has also contributed to better understanding of fundamental processes in metabolism and phenotype behaviour in different environments. This has improved understanding of functional genomics, which deals with the relation between DNA and its direct products in the phenotype. The practical aim of these efforts has been to improve productivity, wood quality and resistance to both biotic (pests and diseases) and abiotic (drought, salinity and cold temperature) stress factors. However, only two countries have so far authorized the commercial use of genetically modified trees. Toxin-producing and salt-tolerant poplars have been permitted for commercial planting in China since 2002 (Liu *et al.*, 2000; Sun *et al.*, 2002; Takabe *et al.*, 2008; Li *et al.*, 2011). In 2015, Brazil authorized a transgenic eucalypt with improved growth. In the United States of America, a petition for the commercial use of a freeze-tolerant eucalypt (Hinchee *et al.*, 2011) was submitted to the authorities in 2013. However, the decision is still pending.

41.   In addition to commercial purposes, forest health is increasingly considered a reason for applying genetic modification technology in forest trees. In several countries, introduced pests and diseases, as well as native ones expanding into new areas as a result of climate change, have devastated large areas of forest, and are even threatening some tree species with extinction. As conventional breeding efforts have proven ineffective or too time consuming as a means of increasing resistance to pests and diseases, attempts have been made to find ways of doing so by applying genetic modification technology. In the United States of America, for example, American chestnut trees have been modified by inserting a wheat gene encoding the enzyme oxalate oxidase into the genome.

Chestnut blight, a cancer disease caused by a fungal pathogen, generates oxalic acid, which weakens cell walls and thus enables other fungal enzymes to kill the cells. The blight arrived from Asia in the early twentieth century and since then has destroyed practically all the chestnut forests in the country. The genetically modified chestnut trees convert oxalic acid into carbon dioxide and hydrogen peroxide, thus increasing the trees' resistance to the blight. The potential for deploying genetically modified trees to restore natural forests has raised a number of ecological, economic and social issues. Because of this, a specific committee was set up in the United States of America to provide recommendations on the deployment of biotechnology to mitigate threats to forest health (National Academies of Sciences, Engineering and Medicine, 2019).

42.   Genetic engineering is much more direct in terms of targeting particular genes or parts of genomes that can be modified so as to give transformants/new individuals with stable expression of desired traits. For more than 30 forest tree species, from genera *Betula, Juglans, Castanea, Populus, Quercus, Eucaliptus* and *Robinia*, genetically modified transformants have been produced, targeting many adaptively important traits such as pest and abiotic-stress resistance (for more information, see Table 4 in Chang *et al.* [2018]).

43.   Poplar, European larch and white spruce have been engineered with a gene encoding an insecticide toxin from the soil bacterium *Bacillus thuringiensis* (Bt). Carnus *et al.* (2006) reported that there were a total of 117 experimental plantations with genetically engineered trees belonging to 24 species around the world. Although the current state of genetically engineered plantations is somewhat unclear, their number has probably increased globally.

44.   As in other subsectors, the CRISPR/Cas9 system has become the most commonly used tool for genome editing in forest trees (Elorriaga *et al.*, 2018). It also offers opportunities for characterizing gene functions in forest trees that have large and sometimes polyploid genomes. Many studies have focused on full or partial inactivation of the genes involved in lignin biosynthesis, for example. The technology is also promising in terms of effective genetic modifications that allow new tolerant and resistant tree transformants and individuals to be produced much quickly than can be done via classical breeding programmes. However, further research is needed to assess how full or partial inactivation of genes involved in wood structure and chemistry might affect long-term tree growth and adaptability. The potential deployment of genetically modified trees has raised concerns about the dispersion of pollen or seed, which might spread selectively advantageous transgenic propagules into natural populations. Addressing these concerns by attaining a stable form of both male and female sterility in transgenic trees before releasing them into open space is not an easy task. Researchers have encountered significant obstacles in the search for sterility, but this work has increased knowledge of the genetic control of reproductive functions and floral genomics (FAO, 2014).

Micro-organism and invertebrate genetic resources for food and agriculture

45.   Developments in biotechnologies are contributing to the sustainable use, conservation and characterization of micro-organisms and invertebrates for food and agriculture. Examples of such technologies and their impacts are described below for insects in general and for selected functional groups of micro-organisms and invertebrates, namely biological control agents, soil microbiomes, rumen microbes and pollinators.

46.   Recent advances in genomic technologies have significantly and cost-effectively facilitated the sequencing of the genome of insect species and their associated micro-organisms. The Sequencing Five Thousand Arthropod Genomes (i5K) initiative[14] aims to sequence and thoroughly analyse the genomes of 5 000 arthropod species, the majority of which are insects. The i5K consortium collaborates with 1KITE,[15] the 1000 Insect Transcriptome Evolution project, the main goal of which is to sequence and study the transcriptomes of 1 000 insect species across all insect orders. It is noteworthy that in the frame of the i5K initiative and with the involvement of the Joint FAO/IAEA Centre (Nuclear Techniques in Food and Agriculture) (AGE) the genomes of several major insect pest species have been sequenced, including the genomes of the Mediterranean fruit fly (*Ceratitis capitata*)

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[14] http://i5k.github.io/
[15] https://1kite.org/

(Papanicolaou *et al*., 2016), the olive fruit fly (*Bactrocera oleae*) (Bayega *et al*., 2020) and several *Glossina* species, including *G. morsitans*, *G. austeni*, *G. brevipalpis*, *G. fuscipes*, *G. pallidipes* and *G. palpalis gambiensis* (International Glossina Genome Initiative, 2014; Attardo *et al*., 2019). In addition, the genomes of key symbionts and pathogens of the above-mentioned species have been sequenced (International Glossina Genome Initiative, 2014; Abd-Alla *et al*., 2016; Papanicolaou *et al*., 2016; Attardo *et al*., 2019; Bayega *et al*., 2020).

47.   Genomic technologies can play an important role in the monitoring of the laboratory domestication of insect populations to which sterile insect technology (SIT) is to be applied, as well as in quality control analysis for such populations (Bourtzis, 2020). Domestication can be monitored on the basis of genetic and symbiotic changes during the process using NGS approaches. Quality control can be done by detecting transcriptional changes at key genes involved in important functions such as fecundity, fertility, longevity, flight ability and mating competitiveness.

48.   The application of biotechnologies, including genomic technologies, has facilitated the development of species/strain-specific PCR diagnostics, which allows the genotyping of mass-reared sterile males released for SIT applications. This has also resulted in the development of PCR assays for the detection of symbionts and pathogens that may affect the efficiency of the mass-rearing process and/or the quality of the mass-reared insects.

49.   Significant progress has also been made in the field of insect transgenesis, including the development of transgenic strains that could be used for sexing in support of genetic methods for population control in insect pests. However, the use of such strains for small-scale field trials or large-scale deployment has raised a number of ecological, social and regulatory concerns.

50.   Genome editing, mainly based on the CRISP/Cas9 system, has revolutionized the field of insect genetic engineering. CRISPR/Cas9-mediated gene editing has been established in many insect species and has been used for both basic and applied research, from fundamental gene function studies to genome/gene editing of pest species of economic and medical importance, including the development of precision-guided SIT. Like transgenic approaches, genome-editing approaches have raised a number of concerns about their potential deployment in the field. However, there is one significant difference: CRISPR/Cas9-mediated gene editing can be very precise and, in principle, can produce non-transgenic genetically engineered strains, strains that could have been produced through naturally occurring spontaneous mutations or chemically induced (e.g. ethyl methanesulfonate-induced) mutations. Recent developments in the field suggest that the CRISPR/Cas9-mediated gene editing can produce such strains quickly and effectively. This could revolutionize the way we develop genetic sexing strains for SIT applications against insect pests and disease vectors, leading from the classical approach (classical genetics combined with irradiation-induced translocations) to a genomic approach, which would be faster and more precise, efficient and cost effective.

51.   Biotechnology and genomic tools (e.g. meta-omics) have the potential to significantly improve pollinator and pollination monitoring and conservation efforts (Creedy *et al*., 2019; Hohenlohe *et al.,* 2021). For example, the field of pollinator taxonomy, which has historically relied heavily on morphology-based identification, has benefited from use of high-throughput DNA-barcoding protocols, which has significantly reduced the time and effort involved in identification (Vamosi *et al*., 2017; Gibbs, 2018). Many DNA barcode sequence data are kept in the Barcoding of Life Datasystems (*BOLD*)[16] – a virtual open repository.

52.   Within disease ecology, metagenomics is a powerful diagnostic tool enabling the sequencing of mixed samples and the examination of gene expression in response to pollinator pathogens and parasites (Doublet *et al*., 2017; Regan *et al*., 2018). The genome of the honey bee (*Apis mellifera*), which was sequenced in 2006,[17] is a key model for understanding aspects of social-insect biology such

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[16] "BOLD is a cloud-based data storage and analysis platform developed at the Centre for Biodiversity Genomics in Canada. It consists of four main modules, a data portal, an educational portal, a registry of BINs (putative species) and a data collection and analysis workbench." (https://www.boldsystems.org/)
[17] The BCM-HGSC (Baylor College of Medicine - Human Genome Sequencing Center) sequenced the honey bee, *Apis mellifera*. The latest version, the Amel_4.5 assembly, is available in GenBank. The version 4.0 assembly was published in October 2006.

as disease transmission, development and gene regulation (Elsik *et al.*, 2014). There are ongoing efforts to obtain genome sequences from other pollinator species (Sadd *et al.*, 2015; Schoonvaere *et al.*, 2018).

53.   More recently, metabarcoding and metagenomics have also been used for analysis of both bee species and their associated pollen – which reveals important information on plant−pollinator networks, pollination systems, evolution and phylogenetics (i.e. genetic lineage) (Pornon *et al.,* 2017; Vamosi *et al.*, 2017; Gous *et al.*, 2018; Darby *et al.*, 2020).

54.   Genetic and genomic techniques for biocontrol agents have been underutilized in the past, with methods for improving biocontrol primarily involving finding more efficient wild species or strains as biocontrol agents (Hassan and Guo, 1991; Hassan, 1994; Nomikou *et al.*, 2001; Hoelmer and Kirk, 2005).[18] Biocontrol agents are now more difficult to import from countries of origin, both because of more restrictive international trade laws (e.g. the Nagoya Protocol [Mason *et al.*, 2018]) and because certain geographical regions strictly regulate which agents can be used (e.g. only local strains originating from the region itself) (Loomans, 2007; Hunt, Loomans and Kuhlmann, 2011). At the same time, increases in organic food production (Willer and Lernoud, 2019) and new policies aimed at reducing synthetic pesticide use (van Lenteren *et al.*, 2018) highlight the need to improve biocontrol efficacy.

55.   Genetic and genomic approaches reviewed in Leung *et al.* (2020) include those in the following categories: biotechnologies for genome sequencing and assembly; gene discovery approaches involving QTL analyses, transcriptomic and proteomic studies, and gene editing; biocontrol agent improvement practices, including MAS, genomic selection and microbiome manipulation of biocontrol agents; and monitoring for genetic variation during rearing and post-release of biocontrol agents. According to the authors, "marker-based methods (such as field-tracking and strain identification) are already being implemented … Others are not yet in use but are imminently possible, such as integrating knowledge of genetic architecture to develop more effective breeding programs … Still others, such as genomic selection, are currently largely in the theoretical realm." The authors also conclude that, while it is contributing to fundamental research, gene-editing technology should not be used in novel biocontrol release programmes, given that the current biocontrol market depends on a reputation for using more traditional genetic methods.

56.   In the past, knowledge about the functioning of complex microbial communities in soils was limited, because only a fraction of the soil microbiota was cultivable (van Elsas *et al.*, 2008). However, the advent of non-culturing methods has allowed researchers not only to identify micro-organisms but also to focus on their communities and interactions. Metagenomics, the study of the entire genome of soil biota, is a powerful tool for assessing the diversity of microbial communities and providing access to new species and genes relevant to biotechnology and agricultural applications (Mocali and Benedetti, 2010). Also, metagenomic sequences can help in the identification of antibiotic-resistance phenotypes (Nesme *et al.*, 2014). Scientists are discovering that the hugely diverse soil microbiome is tied to pathogen control, plant health, increased yield and increased ability to overcome abiotic stress (Fierer, 2017).

57.   This is already reflected in the profusion of selective agricultural practices and microbial products that aim to improve soil and crop health via manipulation of the soil microbiome. The microbial segment is projected to dominate the agricultural biologicals market in the near future, expected to reach USD 10.97 billion by 2026, with a compounded average growth rate of 14.43 percent (MarketsandMarkets[TM], 2020). In addition, microbial products are potential tools in strategies for adaptation to and mitigation of climate change and in ecosystem restoration (Cavicchioli *et al.*, 2019; Sheth *et al.*, 2016; Singh, 2017). Biosequestration and bioremediation innovations, for instance, which rely on soil microbiome functions, have been estimated to have a potential impact of USD 15 billion to USD 30 billion over the next ten to twenty years (MGI, 2020). Key players in the microbial-product market already include large companies such as BASF SE (Germany), Syngenta (Switzerland), Marrione Bio Innovation (United States of America), Isagro (Italy), UPL (India), Evogene (Israel), Bayer (Germany), and Vegalab (United States of America).

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[18] Information and references for this paragraph on biocontrol agents are sourced from Leung *et al.,* 2020.

58.   Deep metagenomic and metatranscriptomic sequencing with metabolite analyses have improved understanding of microbial activities in the rumens of domesticated livestock (Shi *et al.*, 2014).[19] Efforts are ongoing (e.g. Joint Genome Institute, 2017), and could be further increased, to collect data from a more extensive range of ruminants and production systems around the world. Information from existing high-throughput-sequencing-based datasets could be integrated with information on matter and energy flow in the rumen to improve understanding of specific metabolic pathways and genes that may represent targets for rumen modification, ultimately in order to find a balance between food production and greenhouse-gas emissions and improve the sustainability of livestock production.

59.   Based on advances in high-throughput-sequencing technics, pioneering initiatives such as the Human Microbiome Project (HMP)[25] and MetaHIT[26] have developed tools and generated large datasets to enrich knowledge of the diversity of human-associated microbiota. Hundreds of thousands of bacterial genomes from the human gut have been pooled and are accessible in the Unified Human Gastrointestinal Genome (UHGG) catalogues, the most comprehensive sequence resources of the human gut microbiome established thus far (Almeida *et al.*, 2021). Other large projects across the world have generated big metagenomics, transcriptomics and metabolomics datasets from diverse populations (geography, lifestyle, health status and age). They have shown that the gut microbiome has a major influence on our health and that loss of microbial diversity is often associated with disease. Unlike the human genome, the gut microbiome has considerable plasticity and its potential for adaptation to diet and other environmental factors makes it an excellent target for diet-related interventions to improve health (medical interventions, design of new types of food, development of probiotics and prebiotics and dietary recommendations) (Fan and Pedersen, 2021; Sanz *et al.*, 2018).

Plant genetic resources for food and agriculture

60.   Today, over 400 complete genome assemblies of flowering plants (Kersey, 2019) and the sequences of the transcriptomes (i.e. gene coding regions) of almost 1 200 green plant species (Leebens-Mack *et al.*, 2019) are publicly available.[20] Furthermore, there are plans to sequence and characterize representative genomes of 10 000 plants – encompassing every major clade of embryophytes, green algae and protists (excluding fungi) − by 2023 under the auspices of the 10KP (10 000 Plants) Genome Sequencing Project (Cheng *et al.*, 2018).

61.   Though there is scant information on the use of genomics resources in the crop improvement programmes of multinational companies, it is generally assumed that molecular breeding techniques, including MAS, MARS, GAB and genomic selection, have become their methodologies of choice. However, in the relatively recent past, public and not-for-profit research institutions, especially the CGIAR, leveraged publicly available genomics resources to improve the efficiency of the genetic improvement of food crops such as barley, chickpea, common bean, cowpea, groundnut, maize, pigeonpea, wheat, rice, sorghum and soybean (Kulwal *et al.,* 2012). The African Orphan Crops Consortium, which plans to sequence the genomes of 101 under-researched crops in Africa (Ribaut and Ragot, 2019) is expected to increase the repertoire of crops whose improvement will benefit from publicly available genomics resources.

62.   Comparative transcriptome studies can be used to identify differentially expressed genes. As one of many examples, Sultana *et al.* (2020) concluded that differentially expressed genes in Australian wheat varieties under nitrogen stress could be good candidates for use in the development of nitrogen stress-tolerant varieties.

63.   The International Service for the Acquisition of Agri-biotech Applications (ISAAA), which publishes information on biotechnologies, especially genetic engineering, reported that 23 years after the first commercialization of a genetic modification event, 425 such events in 32 plants had been approved for commercialization, planting or importation as food or feed in a total of 70 countries (26

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[19] Information and reference for this paragraph on rumen micro-organisms are sourced from FAO (2019c).
[25] https://hmpdacc.org/
[26] https://cordis.europa.eu/project/id/201052/reporting/fr
[20] For example, https://www.ncbi.nlm.nih.gov/genome/browse#!/eukaryotes/land%20plants

countries, of which 21 were developing countries, had planted the genetically modified crops, while the other 44 had imported them as food and/or feed) (ISAAA, 2018).

64.   CropLife International, a trade association of agrochemical companies, conducted a review of public transgenic breeding programmes in 30 countries across the globe and published an online database,[21] which is searchable by trait. Breeding projects were investigating yield, drought tolerance, pest and disease resistance, abiotic-stress resistance and salinity tolerance. More than ten breeding programmes each were found for wheat, maize, rice and potato, five programmes each for banana and sugarcane and four programmes each for barley, cassava, cowpea and soybean. The most commonly investigated trait was found to be pest and disease resistance (53 projects for 21 crops), followed by drought tolerance (23 projects for 8 crops) and yield (10 projects for 5 crops). This should, however, not be interpreted as a complete overview of public transgenic breeding programmes but rather as a snapshot of trends in a few selected countries.

65.   Genome editing (or gene editing), the term for a new set of techniques that are used to induce precise heritable changes to the genome of a living organism (Hua et al., 2019; Kim and Kim, 2019), is increasingly being used in crop improvement (Bohra et al., 2020). The most commonly used gene-editing techniques are zinc-finger nucleases (ZFNs), TAL (transcription-activator-like) effector nucleases (TALENs) and CRISPR (Gupta and Musunuru, 2014; Hsu, Lander and Zhang, 2014; Trevino and Zhang, 2014; Jiang and Marraffini, 2015; Sternberg and Doudna, 2015; Langner, Kamoun and Belhaj, 2018). Among these, CRISPR/Cas9 and other CRISPR/Cas systems are used most frequently (Mao et al., 2019) and have been used to modify the traits of many plants, including the model plants *Arabidopsis thaliana* and *Medicago truncatula* and others from various genera, including rice, wheat, maize, soybean, sorghum, cotton, rapeseed, barley, tobacco and its close relatives (*Nicotiana benthamiana* and *N. attenuate*), tomato, potato, sweet orange, cucumber, wild cabbage, a wild legume (*Lotus japonicus*), lettuce, common liverwort, petunia, grape, apple, cassava, watermelon and white button mushroom (*Agaricus bisporus*) (Waltz, 2016a; Bomgardner, 2017; Manghwar et al., 2019).

66.   The induced changes include enhanced vigour and improved yield, herbicide tolerance, resistance to diseases, dwarf stature and altered quality attributes (e.g. improved grain protein digestibility and reduced amylose content), albinism, alteration of leaf morphology and changes to days to flowering. Most of the reports in the literature are proofs of concept without indications of plans for commercialization of the products. However, the induction of the waxy starch trait in maize (i.e. reduced amylose and increased amylopectin contents) by DuPont Pioneer is expected to be commercialized through officially released crop varieties by 2021 (Waltz, 2016b; Bomgardner, 2017).

67.   In general, genome editing, especially the most commonly used CRISPR/Cas systems, is relatively inexpensive, and so its continued rapid adoption, including by developing countries, as the method of choice for breeding improved varieties of crops, for example for targeted gene insertion of marker-free DNA in rice (Dong et al., 2020) should be expected.

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[21] https://croplife.org/agricultural-innovation/

APPENDIX

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