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REVIEW

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Advancing genome editing to improve the sustainability and resiliency of animal agriculture

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Abstract

Animal agriculture faces unprecedented challenges, including the need to increase productivity to meet increasing demands for high quality protein while combating increasing pest and disease pressures, improving animal welfare, adapting to a changing climate, and reducing the environmental impact of animal agriculture. Genome editing, in concert with other existing technologies, has the potential to accelerate these efforts. The U.S. Department of Agriculture (USDA) supports research focused on delivering scientific solutions to these national and global agricultural challenges and transferring these solutions to farmers. Genome editing, along with a broad range of other tools, provides an opportunity for scientists, breeders, farmers, and ranchers to meet these challenges and provides additional benefits for society, including healthier and more resilient livestock, while reducing agriculture's impact on the environment. Farmers and ranchers need a full toolbox of existing and innovative options. However, they will not be able to access these tools unless flexible approaches are in place that encourage innovation and allow safe innovations to be used on farms. Genome editing can help us achieve these goals only if global regulatory and policy approaches allow their use in agricultural breeding programs and deployment to farms. The global regulatory landscape for products of genome editing is rapidly evolving, with an increasing number of countries focusing more on characteristics of products and whether they could be achieved by conventional breeding, rather than the technologies used to create them. The livelihoods of people along the agricultural value chain depend upon countries' regulatory and policy choices; regulatory approaches and how they are applied have a dramatic impact in determining what products are developed and who can afford to use these new biotechnologies. We need to step forward and continue the momentum towards regulatory approaches that encourage innovation to ensure continued access to a safe, abundant, and affordable food supply for future generations.

Keywords: Animal breeding, Public policy, Regulatory approach, International trade, Public acceptance, Biotechnology, Livestock, Poultry, Aquaculture

Introduction

Animal agriculture must be increasingly resilient and adaptable in order to support global food security and to protect and improve human health. Farmers need tools to do more with less: to increase agricultural production while fighting emerging disease threats and the effects of climate change while conserving and safeguarding rapidly diminishing natural resources. Meeting these challenges will require investments in research and timely deployment of discovered solutions. Genome editing, while not a panacea, presents a significant opportunity to improve animal health, welfare, and production efficiency; improve human nutrition; and address the causes and consequences of climate change.

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A variety of traits for animals are being developed using genome editing and there is potential for many more (van Eenennaam 2017a; Karavolias et al. 2021). Some traits address animal disease or pests and could reduce need for antibiotics or insecticides. Genome editing could also be used to create healthier and safer food products, or to improve animal welfare. Other traits aim to reduce the environmental footprint of animal agriculture or make animals more resilient to the effects of climate change. The agricultural applications of genome editing are many, but whether these opportunities are realized depends on (1) sufficient investments in research; (2) consumer and market acceptance; and (3) regulatory policy approaches that allow for use of genome editing in agricultural breeding programs.

The U.S. Department of Agriculture (USDA) has more than a century of experience in improving, protecting, and promoting food safety, and decades of experience in regulating products of biotechnology. Across its 29 agencies and offices there is tremendous expertise in animal production, breeding, and health as well as a long history of transferring needed solutions into the hands of farmers. USDA is committed to transforming America's food system by building more resilient local and regional food systems and fairer markets for all producers, ensuring access to healthy and nutritious food in all communities, and growing new markets and streams of sustainable income for farmers and ranchers using climate-smart agricultural practices.

The USDA Agricultural Research Service (ARS) was founded to conduct intramural research to develop and transfer solutions to agricultural problems of high national priority (USDA-ARS 2021). The USDA National Institute of Food and Agriculture (NIFA) was established to fund extramural research on innovative solutions to issues related to agriculture, food, the environment, and communities (USDA-NIFA 2021b). Together, these agencies address key national and global challenges. To be successful, the solutions developed through USDA-supported research must be made available to farmers.

The first genetically engineered animal was produced before the first genetically engineered plant, but the paths for introduction into production have been quite different. Even though animal scientists identified many promising traits over the years, including many that were introduced via genetic engineering, animal producers have so far been unable to reap the benefits of biotechnology. Just as it is crucial for builders and construction engineers to have the best tools available for the task at hand, farmers need access to the full range of tools to address agricultural challenges. Animal scientists and breeders, now more than ever, need genome editing tools to create innovative solutions to the threats facing animal agriculture. Genome editing presents hope for the future, but only if the necessary research investment is paired with policies that enable transfer of these innovations from labs to barns.

Biotechnology terminology[1]

Agricultural biotechnology refers to a range of tools other than conventional breeding that can be used to change the genetic makeup of an organism (see Fig. 1). Biotechnology tools include genetic engineering and genome editing.

Genetic engineering (GE) refers to the insertion of specific genes or gene variants at a random location in the genome using recombinant DNA (rDNA) techniques. Typically, an entire gene (promoter, coding sequence, and terminator) is inserted. Genetically engineered organisms are often colloquially referred to as GMOs or genetically modified organisms.

Genome editing (GnEd) refers to editing a genome at a precise location with enzymes called nucleases, using an organism's own natural DNA repair mechanisms. Because of its precision, GnEd reduces the time and cost and increases the efficiency needed to develop new products. GnEd allows for a wider variety of outcomes, including changes that could have been created with breeding, such as deletions and substitutions.

Both GnEd and GE can be used to develop organisms with genetic material either from sexually compatible relatives (*cisgenic*) or from other species (*transgenic*) (see Fig. 2).

Role of biotechnology in animal genetic improvement

Conventional breeding programs are the backbone of animal genetic improvement, securing incremental, cumulative, and permanent genetic gains. Conventional breeding methods include selective breeding, hybridization, and chromosome set manipulation (described in Fig. 2), as well as assisted reproductive techniques such as cloning, embryo transfer, and artificial insemination. These are all used to accelerate and/or amplify the rate of genetic gain in animal breeding programs. Biotechnologies, including GnEd, allow modification of phenotypes in ways that can reduce the time and cost to accomplish breeding goals. Biotechnologies can be combined with conventional breeding methods and can also be used to

[1] These definitions may differ from colloquial use of the terms, and from how countries define these terms under their biotechnology regulations. Gene editing is often colloquially used interchangeably with the term genome editing.

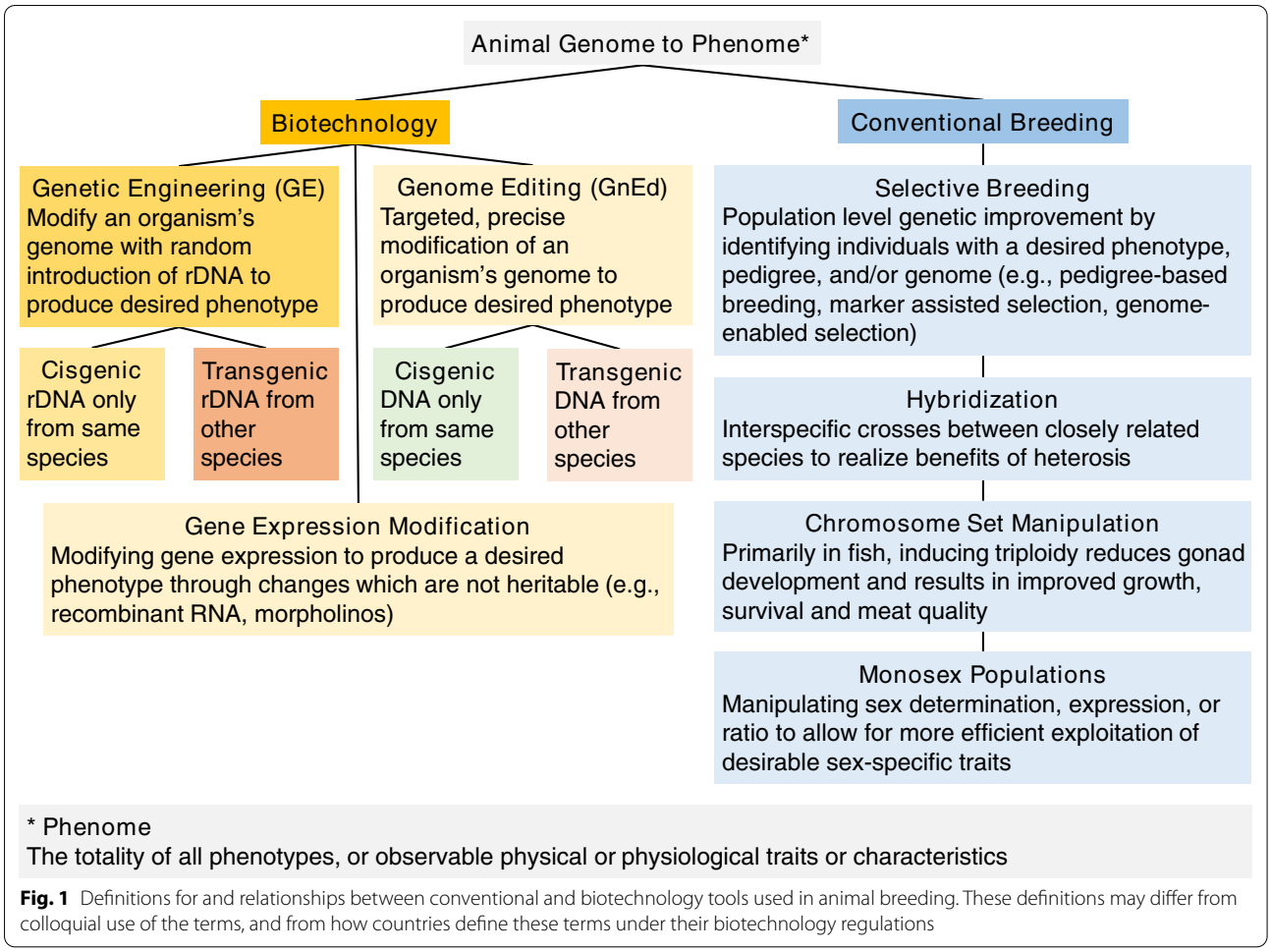

Fig. 1 Definitions for and relationships between conventional and biotechnology tools used in animal breeding. These definitions may differ from colloquial use of the terms, and from how countries define these terms under their biotechnology regulations

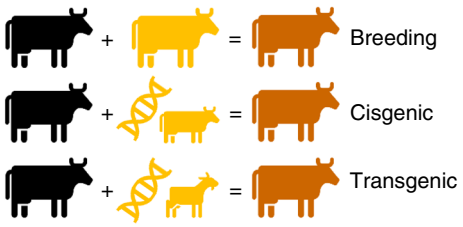

Fig. 2 Hypothetical illustrations show animals developed with: conventional breeding where sexually compatible species are crossed using natural mating or assisted reproductive technologies, such as artificial insemination (top); "cisgenic" DNA sequences where the introduced sequence is from a compatible species and could have been introduced via conventional breeding (middle); "transgenic" DNA sequences where the introduced sequence is from a different species and could not have been introduced via conventional breeding (bottom)

introduce traits that are not available via conventional breeding.

Advances in genome sequencing have led to better understanding of the fundamental biology underlying economic traits (Rexroad et al. 2019) and prediction of phenotypes associated with yield, production efficiency, animal health, well-being, and product quality. High-density sequencing in multiple livestock species has provided baseline information on genes, genome architecture, and genetic diversity. Public and private breeding programs can now rely on this information for decisions involving traits that are expensive or difficult to measure, typically measured postmortem, or expressed in only one sex. By combining this new resource with classical breeding programs, it is possible to accelerate rates of genetic

progress in livestock, including shortening of the generation interval (Kasinathan et al. 2015), which brings particular benefit in dairy cattle and other animals with long generation times. Moreover, genomic information offers useful insights for improvement opportunities through GnEd.

Introducing desirable traits from beef cattle into dairy cattle or from laying hens into broilers can be accomplished by using GnEd without severe setbacks in important traits, such as milk production in dairy cattle or growth rates in broilers, that occur during introgression in conventional breeding programs. For animal welfare traits, GnEd offers novel solutions to address critical aspects of animal husbandry. While conventional breeding programs have documented progress in some animal welfare traits (Pryce and de Haas 2017; Siegel et al. 2019), combining GnEd with conventional genetic selection could speed genetic progress, with simultaneous advances in animal welfare and productivity. GnEd could also provide rapid animal welfare solutions to existing animal husbandry practices that have not been achieved with conventional breeding, such as dehorning in cattle, debeaking in poultry, castrating pigs and sheep, and culling of day-old male chicks in laying hen operations.

USDA's role in animal genetic improvement

Animal genetic improvement programs require highly specialized genetics expertise as well as large investments of time and financial and animal resources. USDA's role has been to support animal genetics policy, education, workforce development, and both intramural and extramural research for new technologies that produce animals with superior performance. To prioritize traits for genetic improvement, USDA regularly convenes government, university, and private sector animal breeders. Economically important traits are often species-specific, but generally are associated with a desire to (1) increase yields; (2) improve production efficiency, such as improved feed conversion ratios; (3) reduce on-farm losses to pests and pathogens; (4) improve animal well-being, including increased stress tolerance; (5) improve the sustainability of production or adaptability to climate change; (6) maintain or improve product quality; (7) increase food safety; and (8) maintain population genetic diversity.

Once priorities are determined, breeders develop approaches that will result in the desired genetic gains. For traits that can be directly and reliably measured in breeding populations, breeders may choose conventional quantitative genetic approaches. USDA-supported animal breeders have clearly demonstrated the benefits of these approaches for farmers and consumers over the last century, including enhancements obtained in the animals listed below. Each of these new animals developed via conventional breeding methods were transferred from USDA or university research stations to farmers, either directly or through a partnership with a private company.

- George Washington is credited with developing mule breeding in the United States (Babb 2021). Mules are produced by crossing a male donkey and a female horse to produce offspring with optimal combined characteristics for labor compared to the parental species. In 1923, USDA published information on mules and mule breeding (Williams 1923).
- The Beltsville Small White Turkey was developed by USDA researchers who began a breeding program in 1937 to create smaller turkeys better suited to meet consumer demands for a family sized turkey by crossing five genetic lines (Livestock Conservancy 2021).
- Brangus cattle (3/8 Brahman and 5/8 Angus) were developed at the USDA Experiment Station in Jeanerette, Louisiana, to combine the heat and humidity tolerance of the Brahman and carcass quality of the Angus (GoBrangus 2008).
- Targhee sheep were developed at the USDA Experiment Station in Dubois, Idaho, to meet producers' need for a dual-purpose sheep with improved meat and wool (Taylor 2018).
- Selective breeding of poultry began in the 1940s, which along with improved nutrition significantly shortened production times, improved feed conversion ratios, increased egg production, and increased both bird and egg size (Hunton 2006).
- Hybrid catfish, a cross between male blue and female channel catfish, have better growth, higher survival, and better yield than purebred lines (Walker 2015). Developed with USDA funding, these hybrid catfish are now raised by more than 50% of the industry.
- A research partnership between USDA-ARS and the Maine Aquaculture Association collects Atlantic salmon phenotypic information from commercial net pen production for use in genome-enabled breeding, with the goal of equitable germplasm distribution across the industry (USDA-ARS 2018, 2019).

In 2008, USDA published the "Blueprint for USDA Efforts in Agricultural Animal Genomics 2008–2017" for animal genome research that prioritized basic and applied animal genomics research in 13 species, aiming to develop and implement new animal breeding tools and resources (Green et al. 2007). Between 2008 and 2017, ARS and NIFA spent ~$500 M on research projects aiming to develop genome sequences, identify genetic variation, map genomes, characterize genome biology, and

implement genomics into selective breeding strategies. Examples include:

- Dairy cattle breeding, with centuries of gains from conventional selection, employed genomic selection to double rates of predicted gain, decrease generation interval, increase selection accuracy, reduce costs for progeny testing, and facilitate removal of recessive lethal alleles (Wiggans et al. 2017).
- In beef cattle, genomic selection in Angus increased accuracy of genetic prediction for young animals, especially for traits with limited phenotypic information such as carcass traits, feed intake, and mature cow size (Moser et al. 2019), and assisted with management of lethal recessive alleles (Upperman et al. 2019).
- In rainbow trout, genomic selection doubled selection accuracy for disease resistance (Vallejo et al. 2017).
- In catfish, genomic selection increased predictive ability 28% for harvest weight and 36% for residual carcass weight (Garcia et al. 2018).

In each of these cases, the research results and new breeds were incorporated into commercial breeding programs. USDA updated and expanded the blueprint in 2018 by publishing "Genome to Phenome: Improving Animal Health, Production, and well-Being—A New USDA Blueprint for Animal Genome Research 2018–2027" that acknowledged successful applications of animal genome research, reflected advancements in genome technologies and expansion of applications of genomic information, and prioritized research activities in all agricultural animals (Rexroad et al. 2019). This updated blueprint added new goals, including enhanced use of genome editing and other biotechnologies, and preservation of genetic diversity.

USDA support for biotechnology

Support of agricultural research "with emphasis on biotechnology" became a priority beginning with the 1985 Farm Bill (U.S. House 1985), including "the effective transfer of new technologies, including biotechnology, to the farming community." That same year, researchers at the USDA Beltsville Agricultural Research Center created the first genetically engineered livestock, a pig with a transgenic rDNA growth hormone gene inserted (Hammer et al. 1985). USDA-funded researchers and their colleagues around the world then began to develop transgenic methods for genetic improvement of pigs, sheep, and cattle in the 1980s and 1990s. The process of creating transgenic animals was inefficient and expensive (estimated to be $60,000 to $300,000, depending on the species) but with increases in efficiencies, there was an expectation that transgenic animals would be used in livestock production (Wall et al. 1997b). Subsequently, the breakthrough development of mammalian cloning techniques using somatic cell nuclear transfer (Campbell et al. 1996) greatly improved the efficiency of rDNA technologies in livestock.

Agricultural biotechnology research, along with agricultural genome research, was among the priority mission areas listed in the Agricultural Research, Extension, and Education Reform Act of 1998 (U.S. House 1998). As with conventional breeding, USDA-funded researchers sought to apply biotechnology to further understand gene function and to obtain desired phenotypes (Murray and Maga 2016). Transgenic technologies, inserting a rDNA construct from non-host genome into a host embryo to obtain a desired phenotype, initially targeted enhanced production or disease resistance (Wall et al. 1997a; Cao et al. 2015; Pursel and Rexroad 1993). Many agriculture-focused GE animals were developed with public funds in the United States and in other countries (van Eenennaam 2017a; Wheeler 2013). Many of these animals had the potential to address issues of concern for both farmers and consumers but became lost opportunities for animal agriculture, as none were able to complete the difficult, expensive and, at the time, uncertain regulatory path to commercialization. Some examples include:

- Mastitis resistant dairy cattle (Wall et al. 2005) and leaner more efficient pigs (Pursel et al. 2004) developed at USDA Beltsville Agricultural Research Center;
- Suppression of prion protein in cattle (Golding et al. 2006; Richt et al. 2007) to create animals resistant to bovine spongiform encephalopathy (BSE);
- Pigs and goats expressing factors in their milk with the potential to improve baby pig survival or enhance human health and nutrition (Bleck et al. 1998; Maga et al. 2006); and
- Disease resistance in catfish (Dunham et al. 2002).

Since its inception in 2008, NIFA, USDA's extramural research organization, has supported research covering several aspects of biotechnology through competitive and capacity-building programs. The 2008 Farm Bill (U.S. House 2008) established and set priorities for the Agriculture and Food Research Initiative (AFRI; USDA-NIFA 2021a), a NIFA-administered competitive grants program. For Animal Health and Production and Animal Products, the priorities specifically included "animal biotechnology" and "identification of genes responsible for improved production traits and resistance to disease." The expectation at that time was that

solutions resulting from animal biotechnology research would be transferred to farmers as both the USDA-Animal and Plant Health Inspection Service (APHIS) and U.S. Department of Health and Human Services (HHS) Food and Drug Administration (FDA) were in the process of developing regulatory approaches for animals developed via biotechnology. However, when there did not appear to be a viable path to commercialize genetically engineered animals for use on farms, funding for agricultural biotechnology research declined. By 2014, no genetically engineered animals had been approved for food use, and animal biotechnology was no longer listed as a Farm Bill priority (U.S. House 2014). Creation of transgenic animals using rDNA and livestock cloning were early technologies that, despite low efficiencies and some scientific uncertainties, helped pave the road for newer methods, such as GnEd, that provide high technical precision and control over the final product.

USDA has long supported research to address priority issues in animal agriculture with a goal to develop solutions that can be delivered to farmers in a timely manner. The increased precision of GnEd techniques makes it easier to introduce genetic changes. They are also considerably less expensive to use than the rDNA technologies that preceded them and research using GnEd is being carried out around the world, including in developing countries (Tan et al. 2016; Mehra and Kumar 2021; Singh and Ali 2021). The promises and opportunities for agricultural applications of genome editing are many, but farmer access depends on the regulatory processes in place. For example, many GnEd applications in animals being developed are for disease and insect control and introduction of these traits would reduce losses by farmers, improve animal health and welfare, and potentially reduce the need for antibiotics or insecticides. Other traits are focused on creating healthier, safer food products and improving animal welfare. Still others aim to produce animals that are more resilient to a changing climate or reduce the environmental footprint of animal agriculture. Some examples of GnEd applications in animals being developed for food and agriculture include:

- Editing the insulin-like growth factor binding protein-2b gene in rainbow trout to characterize protein-level function of duplicate genes, leading to faster and more efficient growth (Cleveland et al. 2018);
- Enhanced genetic control of the new world screwworm (Scott 2014, 2016, 2019, 2020, 2021), a devastating pest for animals;
- Livestock resistant to diseases such as mastitis (Donovan et al. 2014; Ramsay et al. 2017), bovine tuberculosis (Sonstegard 2018), and swine influenza (Kim 2019; Vincent 2019);
- Climate-adaptation traits such as heat tolerant cattle (Sonstegard 2016);
- Animal welfare-associated traits such as elimination of the need to castrate pigs (Donovan 2013; Maga et al. 2018; Berger et al. 2019) or to dehorn cattle (Sonstegard and Murray 2015; van Eenennaam 2017b);
- Surrogate sires as a breeding tool for preserving germplasm and disseminating improved genetics (Ciccarelli et al. 2020), including applications in developing countries where use of conventional breeding tools such as artificial insemination have proven challenging (Patel 2021); and
- Gender selection in cattle (van Eenennaam 2018) for improved production efficiency.

Investing in animal biotechnology research

Public investment in agricultural research provides economic benefits with annual rates of return between 20 and 60% (Fuglie and Heisey 2007). To advance animal biotechnology, investment is needed at all stages of development, including (1) basic research to discover new biotechnology tools; (2) method development to adapt tools to different species; (3) product development, including gene function identification and testing of traits in production settings; and (4) assistance with commercialization, including any required testing for regulatory approvals. Such investment is necessary in part to ensure that farmers in the United States can adapt to new challenges, but also to address global agricultural challenges and to ensure continued competitiveness in the global marketplace.

Many countries are increasing agricultural research investment (Clancy et al. 2016), including for GnEd in animals. However, in the United States, the percentage of federal research funding spent on agriculture declined from 40% in 1940 to just 2% in 2020 (Rowley 2020; AAAS 2021). Research related to agriculture is supported by many federal agencies (Jahn 2020); however, it is significant that only USDA has a mandate to research plants and livestock for the purposes of improving and protecting agriculture. The USDA Science Blueprint includes genome editing of plants and animals as a research priority for 2020 through 2025 (USDA 2019), but funding remains limited.

As described above, USDA agencies have a proven history of delivering quality animal breeding advances that have been useful for farmers. However, USDA projects involving biotechnology are distributed across many subject areas, so determining the number of USDA-ARS and

NIFA projects or the level of funding is challenging. For example, in 2021, USDA-ARS budget levels for livestock production and livestock protection were $127 million and $124 million, respectively (USDA 2021), but existing databases lack the capability to list projects having to do with animal biotechnology or with GnEd specifically. Enhanced cataloging of biotechnology research will enable better classification and coordination of resources at USDA and across federal research funding agencies.

The 2018 Farm Bill established a 3-year pilot program called the Agriculture Advanced Research and Development Authority (AgARDA) for agricultural research and development. Funding for AgARDA was set at $50 million per year. The goals of AgARDA were to (1) prevent, prepare for, and protect against unintentional and intentional threats to U.S. agriculture and food; (2) enhance export competitiveness, environmental sustainability, and resilience to extreme weather; (3) enhance U.S. leadership in research that increases economic opportunities and security for farmers, ranchers, and rural communities; and (4) undertake research and development in areas that industry is not likely to pursue due to technological or financial uncertainty (U.S. House 2018a). Extending AgARDA into a permanent program could complement existing research programs to help USDA advance animal biotechnology along with other agricultural research goals. In 2021, the Tri-Societies[2] expressed continued support for AgARDA and argued for expanding the pilot into an Advanced Research Projects Agency (ARPA) program to fund large, heavily-managed projects that would not otherwise be funded by USDA or the ARPA agencies at the Department of Defense, Department of Energy, or HHS (McMurray et al. 2021).

Such structural and organizational changes as well as additional investment could facilitate agricultural innovation, particularly for animal biotechnology, and help meet challenges such as global climate change and food security. For example, to improve product development and commercialization, there is a need to continue to fund and utilize existing programs for public private partnerships, such as the Foundation for Food & Agriculture Research (FFAR), which pairs federal funding with private funding to address complex agricultural challenges; the USDA Small Business Innovation Research (SBIR) program, which provides small, short-term grants to help bring innovations to commercialization; and the Office of Technology Transfer (OTT), which helps move USDA-ARS research discoveries to the market to solve agricultural problems and expand the economic impact of USDA-ARS research and development. There are also USDA research grants targeted at addressing agricultural challenges in developing countries, including a competitive grants program for research institutions in developing countries to develop agricultural biotechnology (U.S. House 2002). Many applications of USDA-supported GnEd research are well-suited to developing countries; some researchers are already partnering with foreign research institutions and not-for-profit organizations to deliver GnEd solutions to help alleviate poverty and address threats to animal agriculture, such as climate change (Ghosh 2019; Sonstegard 2016).

Public acceptance and market challenges to animal innovation

Significant public acceptance and market challenges must be addressed before GnEd in animals and the resulting products can be commercialized. These market challenges are driven in part by consumer concerns dating back to the introduction of transgenic crops in the 1990s and are influenced by GMO disinformation campaigns. Consumer purchasing decisions are complex; when asked to name concerns about food, consumers identify primary concerns such as taste, price, healthfulness, and convenience (Lusk et al. 2011), followed by secondary concerns such as animal welfare and sustainability concerns, including pesticides; biotechnology is only important to a small percentage of consumers (e.g., Armstrong et al. 2021). Consumers have a very low level of awareness of GnEd, and generally more positive attitudes about GnEd compared to GMOs (Beghin and Gustafson 2021), which may provide opportunities for education. While providing information about a technology can reinforce negative beliefs (Grunert 2002), consumers may be more willing to accept or even pay an increased price for products of GnEd when specific benefits are described (Tallapragada et al. 2021; Caputo et al. 2020).

When evaluating new biotech plants, regulatory systems generally compare food and environmental safety for plants developed using biotechnology with similar conventionally bred plants. While regulators do consider plant health, the safety of a genetic modification to the plant itself has not been a concern of the public. In contrast, the safety of a genetic modification to the animal is of greater interest to the public, as many people have strong emotional connections to animals and express concern for the welfare of farmed animals, although many have little understanding of modern animal production. Consumers may view GnEd or other biotechnologies as allowing for more intensive animal production and may need reassurance about the welfare of GnEd animals (DEFRA 2021). Conversely, public support for GnEd use in animals may increase if specific traits are

[2] American Society of Agronomy (ASA), Crop Science Society of America (CSSA), and Soil Science Society of America (SSSA).

demonstrated to have a positive impact on animal health or welfare, and thus be more acceptable to informed consumers (Tallapragada et al. 2021).

Commercialization decisions by developers and adoption decisions by producers depend on their ability to predict consumer attitudes towards GnEd and other animal biotechnologies. Food manufacturers and retailers may elect to not sell the products of animals or animal lineages in which GnEd was utilized, or to provide "non-GMO"-type labels for animal products produced without GnEd. Markets may choose to self-impose labeling and product segregation systems, even if not mandated, in response to perceived or real consumer demand. Transparency in the development, regulation, production, and commercialization of GnEd in animals—and a focus on GnEd traits that address societal needs—is essential in bringing innovations developed with GnEd to consumers.

Regulatory policy for animal biotechnology

The primary role of regulation is to protect public health and safety. Regulatory risk assessments consider scientific characteristics of a product or group of products, and may include similarity to conventional products; toxicological evaluation of a product or components of a product; investigation of potential environmental impacts; and exposure via food, feed, or in the environment (National Academies of Sciences, Engineering, and Medicine 2016). Regulatory approaches may be standardized for groups of products or determined on a case-by-case basis. Regulatory decisions may be informed by assessments conducted by other countries or groups of countries.

The United States is unusual in not having GMO laws. U.S. federal oversight for biotechnology is a coordinated framework in which each relevant federal regulatory agency implements its authority under existing laws (Unified Website for Biotechnology Regulation 2021), resulting in different processes for plants and animals. Most countries have specific GMO laws, with the same laws governing all organisms—plants, animals, and microorganisms. GMO regulations focus on the process used to create a product, rather than the characteristics of the product itself (Hallerman et al. 2022). Canada has the only purely product-based approach. In some countries, products of GnEd may face additional regulatory requirements beyond those required for similar products created via conventional breeding, even though the final food products may not be substantively different. This could result in products with similar characteristics being regulated differently within a single country.

In addition to regulatory risk assessments for products under GMO laws, some countries have an additional layer where a political-level decision is made for each product or group of products. Sometimes this is part of the official process, as in the European Union (EU), where the scientific risk assessment is separated from the approval decision (USDA-FAS 2020). Political involvement can also be ad hoc, such as when language directed at genetically engineered salmon[3] was included in U.S. Congressional spending bills (U.S. House 2016, 2017, 2018b, 2019). Political-level decisions may or may not be based on the regulatory assessment and might consider issues such as concerns of consumers, needs of domestic producers, and potential economic impacts both domestically and abroad (Smith et al. 2021).

For biotechnology regulations to be truly effective, they must also allow for safe products to be used by farmers and the public. Effective regulatory approaches are transparent, science-based, and risk-proportionate, as well as appropriate for intended use (e.g., an approach designed for biomedical products may not be appropriate for food and agricultural products, since the conditions of use are quite different). Effective regulatory approaches help instill public trust in our food supply and encourage innovation, if regulatory processes are defensible and credible to the public, whose views may reflect values-based issues that fall outside the realm of science-based regulation.

To encourage innovation, regulatory processes must be both timely and predictable. Clearly defined regulatory requirements can inform development and direct research approaches taken and the path to market. Similar phenotypes could be created via different GnEd approaches, and, under some regulatory schemes, different GnEd approaches used to create a specific phenotype could result in different regulatory requirements being applied. For example, under some regulatory approaches, a deletion of genetic material could result in the animal being regulated as a conventional animal, while use of a template (or some types of templates) to achieve a similar phenotype could require additional assessment under GMO regulations. Providing clear information to developers regarding regulatory requirements and exclusions for GnEd applications in animals before they are created can help streamline the development process and can reduce the cost of development, as well as minimize the number of animals required for development.

Regulatory approaches should account for specific characteristics of animal breeding that are not present

[3] Language in Consolidated Appropriation Acts of 2016–2019 under Division—Agriculture, Rural Development, Food and Drug Administration, and Related Agencies Appropriations Acts; Title VII, General Provisions: "During fiscal year 201x, the Food and Drug Administration shall not allow the introduction or delivery for introduction into interstate commerce of any food that contains genetically engineered salmon until the FDA publishes final labeling guidelines for informing consumers of such content.".

in plant breeding. Inbreeding can have a negative effect on livestock and including GnEd as part of a breeding program to introduce new phenotypes could reduce inbreeding compared to conventional breeding programs (Mueller et al. 2019, 2021). For example, regulatory paradigms that require lineage-level approval as opposed to species-level approval will lead to GnEd being cost prohibitive for many livestock and poultry species. Lineage-level approval will either preclude the use of GnEd or force breeders to sacrifice genetic diversity through inbreeding schemes necessary to utilize the few lineages put forward for approval. In swine and poultry breeding programs, organized as multi-layered pyramids, only a small group of founder animals needs to be GnEd. The flatter structures of cattle, sheep, and goat programs will require larger numbers of breeding animals to be edited. If regulatory systems do not allow for approved GnEd traits to be utilized across the target species, minor or rare breeds of economic or cultural value are particularly at risk of being excluded from access to GnEd opportunities. The regulatory approaches that countries choose will determine the availability of GnEd solutions to pressing animal health or environmental challenges.

There are additional impacts of regulatory approaches that may not be as apparent. In conventional breeding programs for food animals, products from animals in breeding pyramids can enter the food chain, allowing breeders to bring in revenue from the sale of animals as new traits are introduced and phenotypes are selected (Van Eenennaam et al. 2021). The sale of food products from conventional research animals at academic and government research institutions helps to support the high cost of animal research.

This has not been the case for most animals created via biotechnologies, including GnEd. The inability for these animals to enter the food chain under some regulatory approaches results in a significant loss of income. Not only are healthy livestock disposed of rather than used for food, but the developer must pay additional costs for the disposal of animals. This is particularly difficult for public sector researchers and represents a barrier to innovation. There is also an emotional cost for researchers and breeders when healthy animals must be destroyed. When non-risk-proportionate regulatory approaches are applied to genome edited animals that are healthy and would otherwise be deemed safe to eat during slaughter inspections, potentially inexpensive solutions to the agricultural challenges faced by the livestock, poultry, and aquaculture sectors will remain out of reach.

Conversely, regulation under existing, stringent food safety laws in place for conventional animals would help to defray the cost of development and reduce waste of wholesome animal products. U.S. regulators recognized that the initial regulations put in place for genetically engineered organisms would be burdensome, especially for academic institutions, developing countries, and small businesses (Maryanski 2006).[4] Modernization of regulatory approaches for these products is necessary, particularly to enable smaller companies and academic institutions to transfer the solutions they develop with GnEd into the hands of farmers and consumers.

Impacts of regulation on access

Countries' regulatory approaches impact the technologies that are available to developers, the products that are developed, and the products that are available to farmers and consumers. The high costs and lengthy timeframe for regulatory approval, along with campaigns by some consumer groups organized against genetically engineered products, have steered breeding companies away from investment in transgenic approaches. Use of these technologies in animals has been largely limited to academic studies of gene function. While some genetically engineered animals have been commercialized, most have been for non-food, non-agricultural applications, and no animals have been approved for production in conventional livestock or aquaculture facilities in the United States. Many research models have been created (Whitelaw et al. 2016) and transgenic, fluorescent fish are popular as aquarium pets.

Thus far, only one genetically engineered animal developed for food and agricultural use has been commercialized.[5] In 1989, AquaBounty Technologies created the AquAdvantage salmon, containing a growth hormone construct from Chinook salmon that improved feed conversion and reduced production time from 3 years to 18 months. In 2010, HHS-FDA determined this fish was safe for human consumption, but it was not approved for food use and import until 2015. In 2021, the genetically engineered fish entered the market in Canada and the United States and was approved for sale in Brazil.

Despite the lack of approvals, many types of livestock and species of fish were created via genetic engineering

[4] 2006 interview of the HHS-FDA Biotechnology Coordinator stating that "The foods developed by this technology [GE] undergo far more testing than all the other foods that enter the grocery store, for food safety. There's really a huge burden that's placed on the developers to use this technology, and that is going to be an issue for developing countries and an issue for small companies. It is, in fact, scientifically difficult to justify a lot of the testing that is being done today for these foods in terms of the public health issues that they actually don't raise. But most of this is now being done to provide confidence to the public that the foods are safe.".

[5] In 2020, HHS-FDA approved a second animal for food use, the GalSafe pig; but this animal was developed for biomedical purposes, such as kidney xenotransplants.

(Murray and Maga 2016; Van Eenennaam et al. 2021). In a well-known case, Environment Canada approved a pig that has less polluting manure in 2009 (Environment Canada and Health Canada 2009). The pig, called Enviropig, was of sufficient interest to farmers that Canadian pork producers contributed to its development. However, without a sufficiently viable path to market, it became apparent that the cost of regulatory approval would be many-fold greater than the initial research investments and the developers lost financial support before they could receive food use approval from Health Canada or HHS-FDA (Nickel 2021).

While animal farmers have been unable to benefit from advances in agricultural biotechnology, crop farmers have had access to traits developed with biotechnology since 1998. The United States is a top producer of genetically engineered crops, with 177 million acres planted in 2019. Globally, 470 million acres of genetically engineered crops were planted in 2019 by about 17 million farmers in 29 countries (ISAAA 2019). Access has been limited to a few high-value species,[6] but genetically engineered crops have helped to improve the socio-economic conditions of farmers, with global economic gains from biotech crops from 1996 to 2018 estimated at US$224.9B (ISAAA 2019). For animal farmers to reap such benefits, there not only needs to be the introduction of new biotechnology tools, such as genome editing, but also a paradigm shift of regulatory approaches.

New regulatory approaches for genome editing

With the advent of genome editing, the regulatory landscape is changing as many countries modernize existing regulatory approaches. Regulatory protection goals remain the same for all foods, whether derived from biotechnology or conventional breeding, with the top priority being to protect the safety of humans, animals, and the environment. New regulatory approaches increasingly focus more on the characteristics (and potential risks) of products of new technologies, rather than on the method used to create them. There is also an increased understanding of the importance of encouraging innovation and of allowing safe products to be transferred to farmers, which will advance addressing significant global challenges and threats to agriculture and food production.

There are essentially two potential regulatory scenarios for products developed with GnEd: (1) to regulate products of GnEd under existing GMO regulations with no exclusions; or (2) to regulate products of GnEd under regulations for conventional animals and products if they do not contain transgenic DNA sequences. If all products of GnEd are regulated by a country as GMOs, then it is likely that GnEd would only be financially feasible for a few high-value crops and few, if any, GnEd applications in animals or specialty crops will be available. However, if GnEd applications in animals that could be achieved via conventional breeding are regulated like products of conventional breeding, then more products, including livestock, vegetables, and fruits, would likely be developed by public institutions and smaller companies. Then more countries could be involved in the development of new products, and more traits would be targeted for regional agricultural problems and local consumer tastes.

Regulatory agencies around the world are considering when to regulate a genome edited product under their existing GMO regulatory process (see Fig. 3 for a summary of potential options). Regulators generally agree that natural mutations and mutagenesis (shown at the top in green on Fig. 3) are regulated as conventional products. Regulators in most countries also agree that transgenic products (shown at the bottom in red in Fig. 3) are subject to regulation under GMO laws. Regulatory agencies are now considering the types of edits that can be made with genome editing, which can be grouped into four categories shown in yellow in Fig. 3: (1) small changes, including substitutions and deletions; (2) short, cisgenic insertions; (3) long, cisgenic insertions; and (4) transgenic insertions. The question is where to draw the regulatory line. For many countries, such as Argentina and Brazil, the line has been drawn between cisgenic changes and transgenic changes (as shown by the yellow dashed line on Fig. 3), such that cisgenic products above the line are regulated as conventional products and transgenic products below the line are regulated under GMO laws.

While too few genetically engineered animals have been approved for agricultural use to draw conclusions about regulatory approaches, one can look to the evolution of regulatory approaches for biotech plants. In particular, new approaches taken by USDA-APHIS and the Ministry of Agriculture, Livestock and Fisheries in Argentina are informative.

Starting in 2011, USDA-APHIS offered the "Am I Regulated" (AIR) inquiry process to review the regulatory status of organisms developed with genetic engineering and determine if they met the definition of a "regulated article" under the legacy regulations (Hoffman 2021; USDA-APHIS 2020). In the petition process, developers could demonstrate that a regulated plant developed with genetic engineering did not pose a plant pest risk, and thus should not be regulated. There were clear differences between the types of developers submitting requests to each process, with less than 5% of AIR

[6] The ISAAA GM Approval Database lists 32 crop species approved for food, feed, and environmental release, but only 14 were planted in 2019. Four major biotech crops were planted on 99% of the total biotech crop area in 2019: soybeans, maize, cotton, and canola (ISAAA 2019).

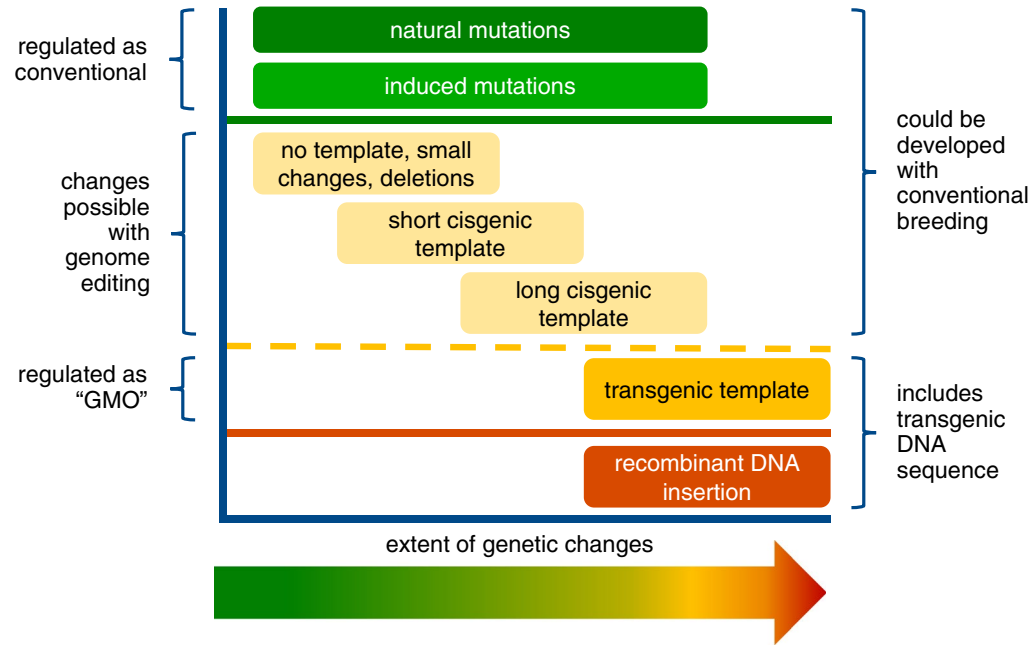

Fig. 3 The type of genetic modifications and mutations that occur in organisms during conventional breeding (in green), in templated and untemplated genome editing (GnEd) applications, both cisgenic (in yellow) and transgenic (in orange), and in genetically engineered (GE) applications (in red)

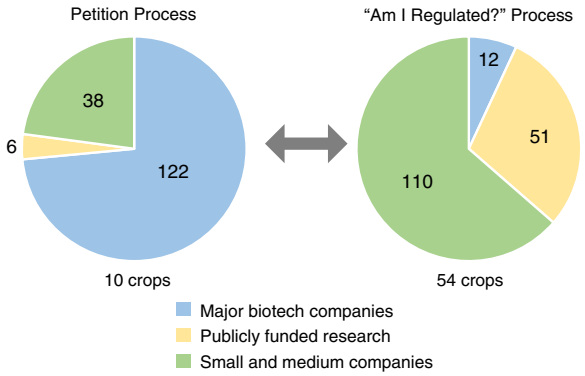

Fig. 4 The types of developer utilizing the two USDA-APHIS legacy regulatory approaches: "Petition Process" (1992–2020) for genetically engineered on the left and "Am I Regulated? Inquiry Process" (2011–2020) on the right, which included 110 plants created via GnEd. Large biotechnology seed companies are shown in blue, small and medium biotechnology seed companies are shown in yellow, and publicly-funded research institutions developing plants with biotechnology are shown in green. USDA-APHIS adopted new processes in 2020

requests coming from major biotechnology companies and more than a third from public research institutions, including some from other countries (Fig. 4). There was also a clear difference in the types of plants and traits submitted. Most petition applications were for just two types of traits (herbicide tolerance and insect resistance) that were incorporated into a limited number of row crops. In contrast, the plant/trait combinations moving through the AIR process were much more diverse and included traits for disease resistance, improved flavor or nutrition, enhanced sustainability, and adaptations for climate change.

In 2020, USDA-APHIS adopted an updated regulatory approach for genetically engineered organisms that improved risk-proportionate regulation and phased out both AIR and petition processes (Hoffman 2021). Although the numbers are currently still small, the new Confirmation Request process appears to allow more small companies and academic institutions to enter the regulatory process, rather than only major biotechnology companies. Herbicide tolerance and insect resistance continue to be important traits to developers and farmers, but now these traits are just two of many that are moving forward through the new USDA-APHIS process, along with GnEd applications in crops developed with public funding (USDA-APHIS 2021).

In 2015, Argentina became the first country to publish their regulatory approach for genome editing, excluding cisgenic products from their GMO regulations (Whelan and Lema 2015). In 2018, Argentina also became the first country to determine that a certain genome edited animal was a conventional animal and therefore did not

require additional GMO regulatory assessments. Argentina's approach for genome edited animals is a relatively straightforward decision tree, in which products of genome editing with a new combination of genetic material (sometimes referred to "foreign DNA") are regulated under their existing GMO regulations; otherwise, products are excluded and do not require additional regulation beyond those required for conventional animals. To further stimulate innovation, Argentina provides developers with a determination prior to development of new GnEd applications, so developers can know in advance of devoting resources to creating GnEd innovations whether the resulting animals and their products would be regulated under conventional or GMO regulations.

In 2020, Argentina published a socioeconomic study on their new regulatory approach that showed similar results as those observed by USDA-APHIS. Foreign multinational companies submitted 90% of products through the former regulatory process, but only 9% of products in the new process. Similar to USDA-APHIS results, 90% of products going through Argentina's GMO approval process were a few high-value row crops with enhanced herbicide tolerance and insect resistance. Under the new approach, applications were more diverse, including traits focused on consumer preference and health benefits (Whelan et al. 2020). Argentina's new regulatory approach facilitated applications from local companies, public researchers, and foreign small and medium companies, and more products were able to enter the regulatory process for the first time. The new policy brought new domestic and international innovation to Argentina.

Many countries with GMO laws have recently adopted approaches similar to Argentina's approach. Brazil and Japan have made "non-GMO" determinations for fish with genomic deletions that increase muscle yield. In 2021, Japan became the first country to have food from a GnEd application in animals, a genome edited lineage of sea bream, marketed to the public (USDA-FAS 2021); a second GnEd application in tiger puffer fish also completed the notification process and is cleared for commercialization (MHLW 2021). The Japanese Ministry of Health, Labor, and Welfare and the Ministry of Agriculture, Forestry, and Fisheries deemed that these genome edited fish lineages have genetic changes that could have occurred via conventional breeding. These fish are the result of public funding and a partnership between universities and a small start-up company that formed in 2019 (Regional Fish Institute 2021). These countries are utilizing new regulatory approaches for GnEd applications in animals that could have been created via conventional breeding under the same food and environmental safety approaches used for conventional animals. This is allowing for GnEd applications in animals developed by public institutions to be commercialized quickly and holds promise for facilitating GnEd solutions developed with public funds to reach farmers and address agricultural challenges in the future.

Regulatory impacts on global trade

To enter any country's market, a product must meet its regulatory requirements and ongoing market requirements. Differing regulatory policies for genome editing and asynchronous approvals for specific GnEd applications in animals across countries have the potential to disrupt global trade in animal products (Qaim 2020). Access to international markets is critical to the US animal agriculture. Exports of beef, pork, and broilers in 2021 accounted for 15.0%, 29.4%, and 16.4% of U.S. production, respectively (USDA-ERS 2022). Therefore, domestic adoption of GnEd applications in animals is contingent on continued access to foreign markets.

Lack of harmonization in market entry requirements such as labeling, product traceability, and segregation requirements will complicate trade and have the potential to stifle innovation. In order to maintain access to foreign markets, animal producers who utilize GnEd will need to conform to the most restrictive requirements of trading partners or develop costly segregation systems for their products. The livestock and poultry industries have historically been reluctant to segment products without significant financial incentives. Foreign markets that are outliers in terms of their regulatory approach for products of GnEd or other market requirements will either drive industry decisions globally if the market is of high value, or risk being cut off from global trade in animal products if the market is not of high value. Some countries have adopted or are considering regulatory policies that would allow for certain GnEd applications in animals and resultant animal products to enter domestic markets without segregation or additional labeling to distinguish them from other animals and their products.

Non-harmonized regulatory approaches in some countries may create challenges for domestic use of GnEd innovations. For example, in the EU all GnEd applications are currently subject to EU GMO regulations, and product segregation would be difficult, especially in cases where the products of GnEd cannot be reliably distinguished from other products by detection methods. While several EU Member States and members of the EU scientific community advocate for biotechnology regulatory reform within the EU (Turnbull et al. 2021) this effort may initially be limited to plants. The extent to which the EU remains a global outlier will impact adoption of GnEd, but there is hope: a European Commission study questioned whether existing GMO laws are "fit for

purpose" when it comes to new breeding techniques like genome editing, and called for additional policy action, particularly for products that could have been developed with conventional breeding (European Commission 2021).

Hope for the future of animal biotechnology

There currently exists a great deal of hope that GnEd solutions will be delivered into the hands of farmers. We do not wish to discount this optimism but note a similar optimism regarding animal biotechnology in the 1980s, 1990s, and the early 2000s. At that time, researchers and the animal industry expected that the products of rDNA technologies would be allowed on the market. The animal industry was preparing for the expected entry of many new animals and products, but only one[7] ever made it to farmers. Both the plant and animal sectors have benefited greatly from advances in genomics, but only certain crops benefited from advances in genetic engineering. Hopefully, history will play out differently for genome editing.

Farmers and ranchers know what works best for their farms. If empowered to do so, many will choose genome editing, in concert with other technologies and conventional breeding, to enhance efforts in increasing productivity of farms and reducing environmental impacts. Responsible and supportive regulation of genome editing technologies will enable animal breeders to more rapidly and successfully develop enhanced breeds with desirable traits; reduce impacts of pests and pathogens; adapt to environmental impacts of climate change; reduce costs and numbers of animals required for genetic improvement; improve animal well-being; maintain product quality; and foster food safety (Rexroad et al. 2019). However, farmers and ranchers will not be able to access these tools unless flexible approaches are in place that encourage innovation, allow their wide use within animal populations, and allow safe products to be used on farms. Regulatory approaches and how they are applied have a tremendous impact in determining what products are developed and who can afford to use new technologies. The livelihoods of people all along the agricultural value chain depend upon the policy choices made by their own country and by other countries.

We hope all countries can agree that regulatory approaches should allow farmers to access GnEd solutions developed at public research institutions, and that any regulatory requirements should facilitate the 3Rs of animal research (replace, reduce, refine) in a way that is efficient. This will ensure that GnEd solutions are available in time to address the problems for which they were created, such as climate change, disease and pest threats, improving animal welfare, or increasing food safety and security. The global regulatory landscape for products of genome editing is rapidly evolving, with an increasing number of countries focusing more on characteristics of products and whether they could be achieved by conventional breeding, rather than the technologies used to create them. Some countries are already moving forward, allowing the marketing of food products from GnEd applications in animals developed with public support. Other countries should follow their lead in developing approaches that treat low risk applications as low risk, allowing farmers around the world to compete fairly.

We find ourselves at a crossroads in the United States today. Many in the U.S. animal agriculture sector have argued that without major policy changes, no animal biotechnology solutions are likely to be available to U.S. farmers and ranchers, putting them at a disadvantage to farmers in other countries. Historically, the United States has been a global leader in development of improved agricultural breeds and breeding tools to enhance genetic gains in fish and livestock. Enabling U.S. researchers and breeders to be leaders in incorporating GnEd tools into our breeding programs will require research investment and appropriate market transparency, and effective regulatory policies are essential to enable safe products to reach the market. Regulatory policies should encourage innovation and provide the opportunity to integrate new innovations into current agricultural production systems. We need to step forward and look to the future so that the next generation of farmers and breeders has more options, not fewer, to better meet current and future challenges, and to do so more sustainably.

[7] HHS-FDA approved recombinant bovine somatotropin (rbST) for use as an animal drug in 1993.

Abbreviations

AFRI: Agriculture and Food Research Initiative; AgARDA: Agriculture Advanced Research and Development Authority; AIR: Am I Regulated; APHIS: Animal and Plant Health Inspection Service; ARPA: Advanced Research Projects-style research agency; ARS: Agricultural Research Service; DEFRA: United Kingdom Department for Environment, Food and Rural Affairs; ERS: Economic Research Service; EU: European Union; FAS: Foreign Agricultural Service; FDA: Food and Drug Administration; FFAR: Foundation for Food & Agriculture Research; GE: Genetic engineering; GM: Genetically modified; GMO: Genetically modified organism; GnEd: Genome editing; HHS: U.S. Department of Health and Human Services; ISAAA: International Service for the Acquisition of Agri-biotech Applications; MHLW: Japanese Ministry of Health, Labor, and Welfare; NIFA: National Institute of Food and Agriculture; OTT: Office of Technology Transfer; rDNA: Recombinant DNA; SBIR: Small Business Innovation Research; USDA: U.S. Department of Agriculture.

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