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National Agricultural Research, Extension, Education, and Economics Advisory Board
Science Advisory Council

USE OF GENE EDITING IN USDA RESEARCH
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Background

The Science Advisory Council was established in FY2016 as a subcommittee of the National Agricultural Research, Extension, Education, and Economics (NAREEE) Advisory Board by the Chief Scientist as a result of recommendations from the 2012 report on Agricultural Preparedness by the President's Council of Advisors on Science and Technology. The Council's charge is to provide advice and guidance, on a scientific basis, on the overall strength, practicality, and direction of agricultural research, including emerging technology and scientific issues and report any findings publicly to the NAREEE Advisory Board.

The USDA Chief Scientist first asked the Council to examine rigor and reproducibility in USDA science. The second was to review the technology of Gene Editing in view of its possible use by USDA to address challenges.

The term gene editing or genome editing is a generally considered a type of genetic engineering in which DNA is inserted, deleted or replaced in the genome of a living organism using engineered nucleases, sometimes referred to using a common description of molecular scissors. The nucleases used in this function create breaks in the target locations in the genome. These breaks are repaired leading to specific edits. There are currently a series of engineered nucleases being used to affect these edits. One of the most commonly known is the CRISPR-Cas system.

In traditional breeding, a desired phenotype is observed and then if the approach is available, the expense warrants it and the tools are available; the genetic basis for the phenotype is studied and elucidated. In the use of a gene editing approach, a reverse of traditional breeding is done in that a sequence of DNA is modified and a phenotypic response is monitored. In this sense of study, gene editing holds great promise to understand better the role of single genes and their possible effect on a product and to modify them for improved human value.

Gene editing is a tool to be used by molecular researchers, hopefully in consultations with breeders, to enhance the search for improved products and solutions. It joins many other tools used by USDA scientists such as selective breeding, cross breeding, marker assisted selection / genomic selection, etc. to improve agricultural production, sustainability and health.

Report Focus

The Science Advisory Council (the council) was asked to reflect on the issue of gene editing in USDA research. The council met by phone and face to face in discussion regarding gene editing technology. The council drafted a version of this report and then met by conference call to discuss the details of the report. The council primarily addressed the following question: What actions should USDA take, if any, to understand better, leverage, and/ or communicate gene editing technology? To help the council address this we broke the issue into six component parts that are presented as questions to be addressed:

1) ***Does USDA need to establish or adopt an existing definition of gene editing, and if so, for what purpose; if establishing a new definition, does this need to relate to other existing definitions?***

From a scientific standpoint, the important aspect of gene editing enabled by CRISPR/Cas technology is its facilitation of the process of changes in construction. The end result of insertion/deletion of these changes in plant and animal genes is not essentially different than previous technologies. The proposed new APHIS rule focuses on the end result of gene editing, and according to the proposed APHIS definition of "genetic engineering", gene editing by CRISPR/Cas would not be regulated[1]. The Science Advisory Council considers this to be appropriate because the end result, insertion/deletions in animal and plant genes, would be appropriate for APHIS review and approval. Oversight by APHIS of animals and plants with altered genomes by CRISPR/Cas technology would help ensure domestic public confidence in these genetically engineered organisms, and it would enhance USDA's global leadership role in regulating genetically engineered organisms, which could facilitate international acceptance of these organisms.

The Science Advisory Council supports the use of CRISPR/Cas technology to facilitate improvement of animal and plant genomes, to improve U.S. agriculture in general and to address problems that limit U.S. agriculture. APHIS should be prepared for potentially increased number of reviews of genetically engineered organisms as the technology is applied more frequently and the technology continues to improve. More proactive education of public on the benefits of gene editing as well as APHIS oversight is recommended to prevent public concern.

2) ***USDA has not in the past focused on the use of specific techniques for plant and animal improvement but has rather focused on developing solutions to particular agricultural problems. Is there an overriding reason for changing that approach in the case of gene editing?***

After discussion, the council unanimously agreed that gene editing should be treated as other techniques and is, in essence, another 'tool in the tool box'. Thus, the current USDA approach should continue with its focus on developing solutions to particular agricultural problems. One advantage of this approach is that the most applicable, cost-effective and least risky approach can be applied to specific problems. Further, regulation of new varietals considers their attributes, a product-based regulatory framework not a process-based one (reference: Precision Genome Engineering and Agriculture: Opportunities and Regulatory Challenges at http://journals.plos.org/plosbiology/article?id=10.1371/journal.pbio.1001877 and Precision Genome Engineering and Agriculture: Opportunities and Regulatory Challenges at https://singularityhub.com/2017/03/28/how-to-feed-9-7-billion-people-crispr-gene-editing-for-crops/) Further, the council strongly concurred that the present approach focuses on the solutions needed to critical challenges in agricultural, which is the most appropriate strategic prioritization of limited resources for success.

The council also clearly perceived the need to educate the public first and apply the technology based on the emerging evidence second. As discussed below, benefits of this technology will only be realized if there is a social license that recognizes the balance of the costs for using gene editing versus the costs of not using it. To this end, the case study surrounding the risk of the Zika virus and the widespread application of the applicable pesticide and its inherent risks to the population far outweighed the negligible risk of using gene-edited biologic controls to limit the spread of the virus.

[1] On March 28, 2018, U.S. Secretary of Agriculture issued a statement providing clarification on the U.S. Department of Agriculture's (USDA) oversight of plants produced through innovative new breeding techniques which include techniques called genome editing. Under its biotechnology regulations, USDA does not regulate or have any plans to regulate plants that could otherwise have been developed through traditional breeding techniques as long as they are not plant pests or developed using plant pests.

This example may be useful in communicating through a specific example the importance and strategic nature of gene-editing approaches to agricultural and public health problems.

3) ***What should be USDA's role in applying gene editing in innovation (developing tools, techniques and methodologies), in meeting needs (applying to specific agricultural problems), both or neither?***

Gene editing, as a tool among many tools, can be useful to researchers and producers. It can help us understand genomes, solve problems in agricultural production systems, and achieve crop production goals.

Most universities and agricultural industries are currently investing in gene editing research and in tool development and application. USDA's role is to fund intramural and extramural research that advances our understanding of genome function, the development of the technology, and the application of the technology to crop production systems and to inform the public and agricultural producers about the extent of gene editing activity and its effect on markets and consumer behaviors.

Gene editing research and development is such a powerful tool, we expect to see it broadly used across major and minor crops. Of course, economically, there may be a move to market where specific germplasm varieties that will carry a positive return on research and development investments.

The choice to utilize gene editing as a fundamental tool has in many ways already been made, but the technology itself remains, as do all new technologies, somewhat controversial. USDA needs to make the technology accessible to all potential users and information about the pros and cons of the technology available and apparent to the general public. Ultimately, USDA needs to be proactive in applying gene editing as an innovative tool and to specifically meet the needs of agricultural producers.

4) ***Does USDA need to make statements on how it plans to use, or is using, gene editing in agricultural research? Why or why not?***

As technology affecting agriculture continues to make important progress, it is critical to ensure that stakeholders, including consumers, understand the benefits and trust the safety of ingredients that arise from the technology. Early education may help stakeholders understand the objectives of the technology and to build an appreciation and confidence when the ingredients make it to the market place.

Science related to food can have a negative and inaccurate perception with consumers. When looked at from the point of view of families and children, food is very personal and emotional. Consumers desire to know more about the source of their food is increasing, and this is likely to continue with younger generations. Having a proactive and transparent approach from the start while communicating in language consumers understand may help form long term trust and support in the technology.

There are many positive examples to help educate stakeholders about agriculture research and the benefits to solving problems regarding climate change, quality, safety and disease, to name a few. The Hawaiian papaya GMO success is one such example.

As we continue to have advance agriculture research, keeping in mind those who will ultimately consume the products is an important part of the process.

5) ***What are the respective roles of the public sector and private sector (as it relates to research) in gene editing, and where do they overlap?***

The council established in deliberations a clear need for BOTH private sector and public-sector access to and development of these tools. The private sector should continue to push the rapid development of new products that are tailored to the market needs and address general societal demands as well as buyer/producer needs. The public sector carries a critical educational/training role across multiple technologies ensuring the workforce of the future is entered into by well-trained scientists who are skilled in the latest technology. Additionally, the public sector has a particularly important role in ensuring access to public products and materials, training and support of pre-competitive research (basic). In the world of major crops, there remains a need for public products that might not normally be produced under typical commercial circumstances yet still fill a valid market need. Illustration of these kinds of needs might include unique variants, organics, and other specialty market products.

6) ***Are there any USDA priorities that can only be accomplished through gene editing that cannot be accomplished through conventional techniques?***

The council concluded that gene editing is not in itself a silver bullet because it is most readily applied presently to simple single-gene traits and may be limited in its application to more complex multi-gene or gene networks. In fact, a common use of the tool will simply be to discover the function of various single genes including confirmation of no impact. Following this 'genetic mapping' of function to gene, further studies will be needed to understand the variability and metabolic flux. Its application to important agricultural challenges will need to be strategic and based on this genetic mapping and metabolic assessment. Given the specificity of the CRISPR/Cas gene editing it will initially be most effective in targeting genes that control major pathways or are rate-limiting in key points in pathways critical to desired traits.

In contrast, complex gene networks often affect yield, major problems of interest, and interactions with multiple environmental factors. Thus, application of gene editing to such multifactorial pathways will require a deeper and more nuanced understanding of such complex networks, metabolomics and fluxes to identify genes to affect outcomes of interest to solve major agricultural problems. Further, multiple gene edits may be required in several key rate-limiting genes once these complex pathways are mapped and understood. Thus, on-going discovery foundational research is simultaneously needed even while initial application of gene editing to singe target genes for more simple traits is studied.
Therefore, both short-term application and long-term exploratory research are needed to realize fully the ultimate potential of gene editing. Even so, a realistic view must understand that confirming the effect of a gene or elucidating a gene network in a research setting, may or may not have a clear practical outcome in the short-term. Gene editing becomes a pathway as well as a tool to find the end product or solution desired.

The time required to elucidate complex genetic networks may exceed in some urgent cases the time available to solve the problems. For example, solving the citrus greening disease is good example of an urgent problem requiring a solution more rapid than gene editing might provide. Thus, the degree of foundational discovery needed, and generation time are critical to consider in assessing the utility of gene editing approaches to the problem. This again emphasizes the nature of gene editing as one of many tools from which the most efficient and effective must be selected in planning the problem-solving research.

7) ***What Priority should USDA give to gene editing in relationship to USDA's existing prioritie, and why?***

After discussing this issue, the council concluded that gene editing will be an important tool to achieve many of its priorities such as increasing food production and improving human nutrition and safety of food products. Like any other research tool, it should be developed and advanced for increased efficiency, accuracy, and understanding of its usefulness and applicability. Acquiring expertise on this tool will allow research in potential cures of genetic conditions, removal of bacterial factors, more targeted development of new drugs in shorter time, decreasing resistance to medications, and crop seed enhancement among others. The limits of its usefulness is still unknown.

The usefulness and limitations of gene editing in agriculture need further definition, therefore, it is critical to continue research in this field and to achieve increased expertise with this tool. For example, the Agriculture Risk Protection Act of 2000 gives the USDA the regulatory power over any genetically modified organism that utilizes the genome of a predefined 'plant pest' or any plant not previously categorized. The white button mushroom in 2015 was the first organism genetically modified with the CRISPR/cas9 protein system that overpassed US regulations, because its development by Yang et al. did not use any potential "plant pest" to insert genes. The USDA sponsored a committee in 2016 to consider future regulatory policy for these new genetic modification techniques, since these new techniques do not use "plant pests" like the GMOs, and, therefore, are not considered under the current "Coordinated Framework for Regulation of Biotechnology." With the emergence of many scientists and engineers using the new technology, understanding its reach, potential and safety for food production and plant enhancement is imperative.

Gene editing is causing a scientific revolution on how we are able to conduct research; therefore, USDA needs to be up front in its utilization and safety. The technology may be the base for a new green revolution with long-term and permanent consequences, and USDA needs to be prepared to use it effectively and foreseen and manage its long-term consequences.

8) ***What should or can REE do, if anything, to enable a more democratized availability of gene editing technologies? (So that it is not only big companies that can use this technology.)***

The Council concluded that gene editing technology is most commonly utilized by research teams at universities throughout the country and private companies. As the techniques are incorporated into training programs for breeders, the technology will become even more widely available and more widely utilized.

USDA REE agencies can fuel the growth and distribution of knowledge about the applicability of the technology, and facilitate broader accessibility to the technology with the following actions:

- Adopt and communicate an agency policy/mission statement that expresses their intention to support research, extension and education about this technology that promotes safety, proper application and increased agricultural productivity.
- Provide intramural and extramural funding for research projects that expand the understanding and applicability of the technology.
- Communicate across potential adopters and the general public about the nature and utility of the technology as well as the science behind the technology, and the opportunities and challenges associated with use of the technology. (See final recommendations of this report for implementation.)
- Communicate with potential adopters and the general public about the relative safety of the

technology.

- Clarify and communicate to the research communities, potential adopters and the general public the product review processes that USDA and the private sector will employ to ensure proper use of the technology.

9) ***Does USDA's role change if gene editing <u>can</u> be detected in some or all products and, if so, how? Does USDA's role change if gene editing <u>cannot</u> be detected in products and, if so, how?***

Gene editing technique is viewed as a transformational tool in agricultural research. For example, the CRISPR technique is so precise that it is considered the least biologically disruptive technique available to date. The USDA rightly considers gene edited crops as fundamentally different from GMOs and therefore does not warrant the same regulatory oversight. The Science Advisory Council of the NAREEE Board recommends that the USDA stay focused on use of gene editing for finding solutions to problems and outcomes rather than regulatory processes.

The Council also concluded that an aggressive education and outreach program about the techniques used to select and bring a new gene edited product to market is critical. Poor communication and public outreach can potentially jeopardize the wide application of this revolutionary tool to address the daunting challenge of meeting the food demands of a rapidly growing world population. The public should not confuse gene edited foods with transgenic foods, although it is very likely to happen in the absence of outreach and education programs. Some practitioners of gene editing technique are apprehensive that the faction of the public that opposed GMOs at the beginning is likely to group these two together and oppose gene edited products as well. Such resistance can greatly impede our nation's ability to be at the forefront of agricultural research and development and likely lose our competitive edge.

The international response in terms of adopting and regulating gene editing in agriculture and food production varies from country to country. Chinese researchers, for example, quickly started adopting CRISPR in agriculture research as soon as the technique's benefits became apparent. Sweden and Argentina have concluded that some mutations induced by CRISPR and some gene edited crops fall outside the definition and regulation of GMOs. Finland and Netherlands appear to be taking a similar approach at least for now, while non-governmental groups in France have shown resistance to this technology. Thus, several European countries, including Germany, are still debating whether or not to regulate gene editing technology in the absence of a clear direction by the European Union[2]. Because CRISPR is accessible and inexpensive, it opens up the possibility of this powerful genetic modification tool falling into the wrong hands. There is a strong need for regulatory agencies to find foolproof ways to prevent misuse of this technology. This is particularly important for the US to be competitive globally, as misuse of CRISPR and mislabeling can possibly lead to exclusion of US products by foreign markets.

10) ***What is USDA's role, if any, in researching and/or communicating the social implications of gene editing? (Note: USDA-NIFA programming in this area at the end of the provided current research information)***

When exploring the social implications, there are many issues involved, but perhaps one key tradeoff

[2] On July 25.2018 the European Court of Justice ruled that organisms obtained by newer mutagenesis techniques that alter the genetic material of an organism in a way that does not occur naturally, such as genome editing, are GMOs and are subject to the obligations laid down by the GMO Directive.

is to show that the benefits to society outweigh the risks. This requires transdisciplinary research to assess how consumers perceive risks and benefits (sociology and behavioral economics), potential productivity gains and ecological risks (biological sciences), as well as economic winners and losers, but such research requires a shared agenda among research teams. It may be that the traditional choice to commercialize and release safe products, might be adapted to include more social welfare considerations which include public release of alternative products. The mixed public attitude regarding GMOs suggests that people are likely to accept gene-edited products but only if there is a dependable authority to substantiate the safety and educate the public. If so, further development, adoption and food business promotion may face a bottleneck that is somewhat constrained by uneven consumer acceptance of transgene-free food crops developed by genome editing.

Developers of the technology should be encouraged to produce products with traits that would foremost satisfy consumer or social health needs and to create clear beneficial outcomes for the greatest share of the market/citizenry as possible. Moreover, better risk–benefit communication should be formulated as the government considers their regulatory status and establishes appropriate regulations. If careful risk–benefit communication is used at each stage of the development of transgene-free products, it will increase the chances they will be fully integrated into the marketplace and society.

11) ***What actions, if any, need to be taken by the Chief Scientist to address issues raised in this report and are yet to be addressed?***

The Science Advisory Council recommends that the Chief Scientist should take the following actions:

a. The Office of the Chief Scientist should review all USDA agencies and their current efforts to communicate about Gene Editing technology and encourage each appropriate agency to establish education and outreach efforts and programs to help explain the use of it as a tool.

b. The Office of the Chief Scientist should encourage the use of multiple appropriate technologies to develop the best, effective and safe products to market

c. The Office of the Chief Scientist should develop a comprehensive outreach strategy on gene editing, taking into consideration the public's ethical, moral, cultural, philosophical, theological and ecological positions and beliefs.

d. In addition, the guidelines established by agencies regulating gene editing in agriculture and food production should be shared by the Office of the Chief Scientist beyond the confines of the scientific society through outreach programs to enable the public to have difficult questions addressed and to ensure the public's trust in regulatory measures.

e. There is a general public perception that the scientific community is not accustomed to effectively communicating the details of research, its benefits, and more importantly, its potential unintended consequences to the public. The Office of the Chief Scientist and the Chief Scientist should urge land-grant institutions, and everyone involved in agriculture and food production who receive USDA funding, to aggressively campaign in favor of gene editing as an effective tool and recognizing its benefits. Strategic communication and sufficient follow-up are necessary while interacting with reporters to prevent distortion of science due to oversimplification of stories. Some experts have recommended active participation of all stakeholders in online discussions about the benefits of gene editing. Performance evaluations and reward systems for scientists should reflect the value and emphasis placed on public outreach as well.

f. It is essential that the Office of the Chief Scientist be open in communications about benefits and risks of gene edition technology, including any chances of off-target mutations. This should be done in a manner that respects and guarantees the public's right-to-know.

g. The Office of the Chief Scientist and the Chief Scientist must also foster communication between public and biotech companies regarding the gene edited products released into the market.

Report Developed by the Science Advisory Council, a Subcommittee of the NAREEE Advisory Board

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