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Presentation before the ADVISORY PANEL TO BETTER UNDERSTAND AND MAKE RECOMMENDATIONS REGARDING THE IMPLICATIONS OF GENOME-EDITING TECHNOLOGY TO THE CITIZENS OF THE STATE

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Good afternoon, Senator Claxton, Representative Zager and members of the advisory panel, my name is Laura Reinholdt and I am Associate Professor of genetics at The Jackson Laboratory. The Jackson Laboratory is an international genetics and genomics research institution, headquartered in Bar Harbor, with other Maine-based facilities including in Augusta and Ellsworth.

I'm pleased to have the opportunity to speak to you today and would like to thank the panel for their service and interest in learning more about gene editing.

Public policy and ethical discussions of scientific technology and its potential impact on society should include and be informed by, scientists, policy makers, and the general public. Scientific and societal consensus should be the goal, and it should be an on-going discussion as technologies and our knowledge about them evolves.

For these reasons, I applaud the foresight of the Maine legislature who voted to establish this advisory committee, and congratulate co-chairs Senator Claxton and Representative Zager, for sponsoring the legislation.

In this presentation, I was asked to answer the following two-part question. "What should the State of Maine do regarding gene editing within your field of expertise in order to best benefit Mainers in the next five years and subsequently, over the next generation?."

In answering these questions, I offer my perspective on the positive, transformational impact of gene editing technology in biomedical and clinical research broadly, and locally, here in Maine.

I have spent the majority of my scientific career here in Maine, having moved here for a post-doctoral fellowship opportunity in 2001. I became a scientist because I was always fascinated by the natural world, and when I came to understand genetics, I recognized it as the biochemical thread connecting us all, dictating patterns in nature, and across generations. I knew I wanted to be as close to that work as possible and really didn't dream that I would eventually be where I am today. I'm incredibly grateful to all of the mentors that helped get me here, many of whom established their careers here in Maine.

In addition to my personal background, my presentation also reflects the collective experience of my colleagues at The Jackson Laboratory, a non-profit institution at the forefront of biomedical research in Maine. The laboratory holds over 100 active NIH grants and employs over 1,800 people at three locations: the headquarters campus in Bar Harbor, the Maine Cancer Genomics Initiative in Augusta, and at an innovative production facility in Ellsworth, constructed with matching, competitive funding from the Maine Technology Institute. The Laboratory invests substantial capital every year in research tools used by scientists at each of these locations in our mission to discover precise genomic solutions for human disease. This work is vital to enhancing our quality of life through better health and high-quality jobs. Life sciences research and development is essential to Maine's innovation economy and is highlighted in numerous recent reports including the Maine Economic Development Strategy 10-year plan and reports from the Maine Development Foundation, Maine State Chamber of Commerce, and Educate Maine. Maine's ability to sustain and grow its innovation economy is related to our continued access to critical technology including gene editing, the focus of today's discussion.

During my career, I experienced two technological inflection points – these were next generation sequencing technologies and CRISPR/cas9 based genetic engineering.

Next generation sequencing technologies have allowed us to move from sequencing a single genome for $2.7 billion dollars in 13 years to sequencing a single genome in under a day for around $1,000.

We call these technologies disruptive because they open up completely new industries and fields of research. And that has certainly been true for genome sequencing. The results are tens to hundreds of thousands of genomes revealing incredible genetic variation across humans and across all other species. As scientists could begin to ask which of these variants cause disease, which of them variants make us susceptible or resistant to certain environmental exposures, infection, which of them determine if a drug for some and not others, but we would need significant innovation in genetic engineering technologies to begin to tackle these questions.

The next technological inflection point that occurred during my career was gene editing – particularly CRISPR based genome engineering. This was the disruptive technology that would allow us to functionalize the billions of genetic variants revealed by next generation sequencing technologies. Not only would be able to know what to engineer, we had the technology to accomplish that engineering at scale.

Considering these watershed advancements, my peers in the scientific community quickly recognized the potential societal impact of 'easy' genetic engineering if it were to be applied to engineering of sperm or eggs – these "germ cells" across all species carry our genomes to the next generation.

For example, one of the first therapeutic applications of gene editing was the correction of the single mutation that causes Sickle Cell Disease in the red blood cells of a patient. Editing a patient's red blood cells effects only the patient; editing the same patient's sperm or egg cells would pass the modification on to the patient's children and to subsequent generations. This kind of gene editing - also known as "germline editing" quickly became a topic of scientific debate.

Ultimately, scientific organizations like the National Academy of Medicine, National Academy of Sciences, NIH and the World Health Organization have articulated a moratorium on germ line editing. It was, in fact, the inventors and users of the technology who were the first to self-regulate. Later, government regulation in some countries would follow suit. For example, the US Food and Drug Administration will not approve a gene therapy where there is risk of introducing heritable changes to the DNA.

With oversight including from within the scientific community and at the federal level, gene editing is a state of the art tool that is now used extensively in biomedical research. I'd like to offer three examples of how my colleagues and I use this technology in our labs at The Jackson Laboratory:

- *Discovery* (*Which genetic variants are important?*): High throughput gene editing in cell lines (which are cells grown and maintained outside of an organism) and in simple model organisms like mice allows us to ascertain function for the millions of genetic variants that have been discovered by genome sequencing projects. This simply could not be done efficiently prior to CRISPR-Cas9 and other gene editing technologies. In this application, CRISPR allows us to identify the most important, impactful genetic variants by editing them and studying the resulting physiological consequences.

- *Disease modeling* (*Which interventions / therapies are most effective in curing a genetic disease?*): Editing the genomes of mice and other model organisms to introduce the genetic variants that cause disease in people gives us an experimental system where we can test interventions in a model carrying the same disease-causing mutation. This is what we mean by "precision modeling". The specific mutation in the patient can be engineered into the mouse. At JAX we have the Center for Precision Genetics as well as the Rare Disease Translational Center – both are focused on building these important disease models, which are then distributed throughout the scientific community for pre-clinical research.
  - The number of new CRISPR-generated mouse models of human disease stewarded by The Jackson Laboratory has grown by two orders of magnitude over the last 5 years.

- *Therapy* (we can use gene editing in vivo, in cells and tissues of the human body to 'correct' a disease-causing variant or replace the affected gene product. These approaches are extensively tested in animal models, that are often CRISPR-engineered themselves. In, the laboratory mouse is critical in this pre-clinical research because like humans, they are mammals, we can manipulate their genomes, we can control their genetics as well as their environment. At JAX we have the Somatic Cell Genome Editing center that is NIH funded, completely focused on advancing methods for somatic gene editing as therapy and the requisite mouse models.
  - The next step in the process of developing gene therapy is to use this preclinical knowledge for further testing in primates or direct investigational new drug applications / clinical trials in human patients as we advance cures for genetic disease.

In these examples, gene editing is being used to discover gene variants that protect or cause disease, gene editing is being used to model these genetics in model organisms, and gene editing is being used to develop potential therapies. All of this is happening at The Jackson

Laboratory, where gene editing technology is helping us advance our mission to discover precise genomic solutions for human disease.

Coming back to the original questions – “What should the State of Maine do regarding gene editing within your field of expertise in order to best benefit Mainers in the next five years and subsequently, over the next generation?”

Within the next five years, and in concurrence with Dr. Ben King’s presentation, The State of Maine should promote awareness and education in life sciences in both schools and community organizations. To build on Dr. King’s recommendations, one way the state can do more to invest in K12 education is to support organizations and programs that are already working to support teachers and schools, and usually bringing federal dollars into the state to do so. Existing programs such as The Jackson Laboratory’s Teaching the Genome Generation, which has reached over 9,000 students at 61 Maine high schools; or, the Personal Genetics Education Program’s Faith Partnerships, which engages faith communities on how we make collective decisions about whether and how to proceed with gene editing, can be expanded to reach more students, more schools, and more community organizations in the state.

In my view, most Maine citizens are not well informed about biomedical technology or have adequate resources to learn more or engage in conversations about biomedical research, let alone specific technology like gene editing. In the near term, this advisory committee should be confident in recommending policy that enhances education and awareness, knowing that stringent federal regulations limiting the use of gene editing technology already exist.

Also in the short term, I suggest the state build and sustain an environment where discussions and panels like this become the norm, and not the exception. For example, my colleagues and I are excited to see that Maine will establish a Rare Disease Advisory Council to discuss and help solve issues that impact patients and caregivers of people with rare disease (usually children). I think in the long term, we’ll see an intersection of the gene editing technology discussed in the context of this panel with the interests of the rare disease community.

Finally, over the long term, Maine should invest in medical research talent and infrastructure such that patients are not prevented from accessing future genomic treatments due to lack of proximity to a major research hub, such as Cambridge or Boston. I suggest Maine make it a state priority to bring these medical centers closer to patients by investing in an environment where medical research can be performed, and clinical trials delivered closer to home.

Thank you for the opportunity to present before you today. I again want to thank you for your service and for bringing this important conversation into the public sphere.