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GENE EDITING TECHNOLOGY: INNOVATION AND IMPACT

HEARING

OF THE

COMMITTEE ON HEALTH, EDUCATION, LABOR, AND PENSIONS

UNITED STATES SENATE

ONE HUNDRED FIFTEENTH CONGRESS

FIRST SESSION

ON

EXAMINING GENE EDITING TECHNOLOGY, FOCUSING ON INNOVATION AND IMPACT

NOVEMBER 14, 2017

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C O N T E N T S

STATEMENTS

TUESDAY, NOVEMBER 14, 2017

GENE EDITING TECHNOLOGY: INNOVATION AND IMPACT

Tuesday, November 14, 2017

U.S. SENATE,
COMMITTEE ON HEALTH, EDUCATION, LABOR, AND PENSIONS,
Washington, DC.

The Committee met, pursuant to notice, at 10 a.m. in room SD–430, Dirksen Senate Office Building, Hon. Lamar Alexander, Chairman of the Committee, presiding.

Present: Senators Alexander [presiding], Murray, Collins, Young, Scott, Casey, Warren, Kaine, and Hassan.

OPENING STATEMENT OF SENATOR ALEXANDER

The CHAIRMAN. Good morning.

The Senate Committee on Health, Education, Labor, and Pensions will please come to order.

Senator Corker is chairing a Foreign Relations Committee hearing down the hall about when the President of the United States can use nuclear weapons.

We are taking a different tack today.

We are looking at something quite different and extremely interesting to me. It is about gene editing and a new technology with amazing potential that raises important ethical questions as well.

Senator Murray and I will each have an opening statement, then we will introduce the witnesses. After the witnesses' testimony, Senators will each have 5 minutes of questions.

Eric Lander, a leading geneticist and mathematician, who was integral to the Human Genome Project said, "It is hard to recall a revolution that has swept biology more swiftly than CRISPR."

Today, we are looking at this remarkable technology to edit genes that has the potential to treat devastating diseases, including those that currently have limited treatments or cures.

While CRISPR is not the only way to edit the human genome, it is one of the most exciting and talked about ways in the medical research community. It is a relatively new technology. It essentially uses molecules that can be targeted to act as scissors to cut and edit genes.

While CRISPR acts as the search function, it goes and finds the mutated gene—Cas9 is the tool that deletes the disease-causing gene—inserts new genes or repairs mutated genes. In a way, it is like cutting and pasting in a computer document.

That may be an oversimplification, but CRISPR technology is less expensive, more precise, and more readily available to scientists all over the world than other gene editing technologies.

A "New York Times" story in August reported that CRISPR can be used to do something as frivolous as making yeast glow like jellyfish to something as serious as making real strides against diseases, such as correcting the gene that causes sickle cell anemia.

While CRISPR was developed in 1993, its use was perfected for humans in 2013, only 4 years ago. Its most widespread use until now has been in agriculture. Disease resistant wheat and rice has been created using CRISPR, and CRISPR has been used to modify tomatoes and soybeans to improve yields and create healthier soybean oil.

There is the potential to create crops that can produce higher yields, are able to live through a drought, and have increased nutritional value. Some researchers are even looking at ways to make better tasting crops.

CRISPR's use in humans is more recent, but the possibility of the diseases it could treat, and the lives that could be improved, is remarkable.

According to the Centers for Disease Control and Prevention, sickle cell disease occurs in about 1 out of every 365 African-American births. One of our witnesses today will be able to speak to research on how CRISPR can help with this devastating disease.

Editas Medicine, who is represented by one of our other witnesses today, sees the potential to treat blood disease that today are currently only treatable through blood transfusions and bone marrow transplants. Using CRISPR, the genes causing blood disease could be edited and re-administered to treat the disease more safely and effectively.

For cancer patients, CRISPR could improve the amount of time immune cells are active in fighting tumors. The possibilities could go on further.

If we could eventually identify the gene mutation that, for example, shows a predisposition to Alzheimer's, could we edit that gene and prevent the suffering and heartache that Alzheimer's causes?

While CRISPR, and other gene editing technologies, could transform human health, it is not hard to see how we can quickly get into societal and ethical issues.

The technology could lead to permanent changes in the human genome. There is even the possibility of making changes in embryos to create so-called "designer babies."

In the hands of our adversaries, CRISPR poses national security concerns through the potential to produce new biological weapons. In February 2016, former Director of National Intelligence, James Clapper, added gene editing to a list of "weapons of mass destruction and proliferation."

I know the leaders at Oak Ridge National Laboratory, and other places in the intelligence community, are having classified discussions similar to the one we are having today.

Part of our job on this Committee is to learn about new technologies, to lead the discussions with experts about the implications of these scientific advancements, and to ensure that the Na-

tional Institutes of Health and others have the proper authority to oversee and conduct research.

Our Committee has a long history of working in a bipartisan way to pass legislation that helps advance biomedical research to improve the health of Americans, through the 21st Century Cures Act last year and the reauthorization of the Food and Drug Administration user fees this year.

Senator Murray has had a special role in that. Over the last 3 years, the Appropriations Committee—on which others of us serve—has added $2 billion a year to the National Institutes of Health and then another $4.8 billion through the 21st Century Cures Act, and I thank her for that.

I am also a member of that Appropriations Committee. I am a strong proponent of what we just described and CRISPR is just one of the amazing discoveries that have come from basic research funded, in part, by the Federal Government.

Today's hearing is truly a hearing. I intend to do more listening than talking, and I appreciate our panel taking the time to discuss this promising technology today.

Senator Murray.

OPENING STATEMENT OF SENATOR MURRAY

Senator MURRAY. Well, thank you very much, Chairman Alexander.

Thanks to all of our witnesses, and our colleagues, for joining us today.

About a year ago, Congress passed the 21st Century Cures Act after 2 years of work from this Committee, boosting funding for lifesaving research that will help drive the next generation of innovative treatments.

Nearly $5 billion more will be invested to tackle our most challenging scientific and medical puzzles. I am really pleased today that we have an opportunity to talk about one piece of this puzzle that is truly exciting and promising.

Gene editing technology has the potential to be used as a tool to tackle difficult research questions. A treatment for serious genetic diseases like sickle cell and Huntington's, an approach to engineering our own cells to fight cancer and infections, and a new way to help stop the spread of infections, vector-borne diseases like Zika and Malaria.

I am proud that my home State of Washington is leading the way in advancing this technology. At Seattle Children's Ben Towne Center for Childhood Cancer Research, scientists are harnessing patients' own immune system to cure cancers that were not responsive to other types of therapies.

I have had the opportunity to meet with researchers from Juno Therapeutics, which is working to develop T-cell therapies for a number of cancers.

Though we still have much to learn about harnessing the power of T-cells, researchers like Dr. Porteus and companies like yours, Ms. Bosley, have already begun to apply gene editing technology to T-cells. I will be interested in hearing from both of you about how CRISPR technology is supporting that work.

As we all know, mosquito transmitted viruses like Zika have had a devastating impact on patients and families across the United States and throughout the globe. The Bill and Melinda Gates Foundation is doing promising work on strategies to combat the spread of those viruses, which includes harnessing CRISPR gene editing technology to change the genetic material of particular mosquitoes, for example, causing mosquitoes to only have male offspring, which could eventually eradicate this particular species that serves as vectors for the viruses.

Those are just a couple of examples, and I have no doubt there are ways CRISPR technology could help patients and families that we have not even begun to think of yet.

I am glad that bipartisan work on this Committee has enabled us to enact policies in 21st Century Cures and the FDA user fee reauthorization that will help continue to spur innovation.

In addition to investing more in research at the NIH, we ensured federally funded research includes diverse populations who have historically been underrepresented in clinical research. We put in place new protections to keep research subjects' genetic information private and given the FDA new hiring authority to make sure we have the best minds at the agency to help foster the development of this exciting new technology.

There is certainly more to do and I am interested in your perspectives on how Congress can continue to best support progress while protecting patients' health and safety.

It is absolutely critical that in continuing to make medical advancements, our country upholds the highest standards of ethics and consumer safety, and helps to ensure those standards are being followed around the globe.

Dr. Kahn, you have done extensive work on the ethical questions surrounding biomedical research. I am glad you are here today to help share your expertise with the Committee today because in order for congressional oversight to be valuable, scientific consensus and standards must drive our decision making and approach.

I will close by saying I continue to be inspired and heartened by the bipartisan commitment to investing and supporting biomedical research. I hope, as new opportunities and technologies like CRISPR emerge, we can build on the foundation we have established and work together to support those efforts and prioritize patient safety and health.

Thank you very much, Chairman Alexander, for holding this hearing and I look forward to it.

The CHAIRMAN. Well, thank you, Senator Murray.

I would say, just for the record, this is one more bipartisan hearing which, for the uninitiated, means that Senator Murray and I agree on the subject. We agree on the witnesses, and that is the way we do most of our hearings, and that is the way we usually do our best work.

We welcome our witnesses. Each will have up to 5 minutes. If you could compress your thoughts into 5 minutes, that will leave Senators more opportunity to ask questions.

I am pleased to welcome the three of you.

The first witness is Dr. Matthew Porteus, Associate Professor at Stanford University. His lab is using gene editing technology to develop potential cures for genetic diseases such as sickle cell, cystic fibrosis, HIV, and Huntington's disease. He is a member of the National Academy's Committee on Human Gene Editing, which published a report earlier this year.

Senator Warren, would you like to introduce the second witness?

STATEMENT OF SENATOR WARREN

Senator WARREN. I would. Thank you very much, Mr. Chairman.

Massachusetts researchers and companies are at the forefront of the development and application of gene editing technology. So I am very pleased that Katrine Bosley is joining us here today to share her perspective.

Ms. Bosley is the President and CEO of Editas Medicine, a company based in Cambridge, Massachusetts that is developing therapies based on the CRISPR gene editing technology.

Editas' work tackles a wide range of genetic diseases including Duchenne muscular dystrophy, sickle cell disease, cystic fibrosis, and Usher syndrome.

Ms. Bosley also serves as a board member of the Biotechnology Innovation Organization. She has been working in the biotech industry for more than 25 years.

We are fortunate to have her here today to discuss the use of gene editing technology in drug development.

Thank you, Katrine, and welcome.

The CHAIRMAN. Thank you, Senator Warren, and welcome, Ms. Bosley.

Our third witness will be Dr. Jeffrey Kahn. Dr. Kahn is the Director of Johns Hopkins Berman Institute of Bioethics and he is Professor in the Johns Hopkins University School of Public Health.

His research interests include ethics and emergency biomedical technologies, a topic that is important for our hearing today.

He is an elected member of the National Academy of Medicine and was also a member of the National Academy Committee on Human Gene Editing.

Welcome to all of our witnesses.

Dr. Porteus, let us begin with you.

STATEMENT OF MATTHEW PORTEUS

Dr. PORTEUS. Chairman Alexander, Ranking Member Murray, Senate Committee Members, and the staff.

Thank you very much for this very great honor to come and speak to you regarding these exciting new technologies of genome editing, the CRISPR/Cas9 tool, and the potential to cure what is now currently incurable.

Let me briefly introduce myself. I am a physician scientist who is trained as a pediatric hematologist/oncologist, which means I take care of children who have blood diseases and cancer. When I wear my M.D. hat, I actually work on the bone marrow transplant unit at the Children's Hospital at Stanford.

Bone marrow transplants are an intense and complicated procedure in which we take the blood stem cells from one person and give them to the patient. By using this procedure, we can cure chil-

dren with cancer, bone marrow failure syndromes, and other inherited genetic diseases.

But when I put my scientist hat on, I run a research lab within the Department of Pediatrics in the Stem Cell Biology Institute at Stanford focusing on developing genome editing to cure genetic diseases. It is on that I am excited to speak to you about today.

I have several affiliations with groups that are interested in this topic, but everything that I will say today represents my viewpoint alone. There is a reasonable chance that at some point, I will put my foot in my mouth, and I apologize for that in advance.

Unfortunately, there remain tens of millions of people in the United States, and hundreds of millions of people around the world, who are born with genetic diseases; most of these patients are actually children.

These are diseases that are caused by single mutations in single genes that lead to devastating consequences. Almost all of these diseases have no good treatment, much less no good curative therapy. As has been mentioned by the Senators, diseases such as sickle cell disease, cystic fibrosis, hemophilia, and Huntington's disease are all such diseases.

Genome editing, which is simply a more precise form of gene therapy, is a potentially ideal cure for these monogenic diseases because it gives us the ability of converting disease causing mutations in DNA back into non-disease causing sequences. It is a method to correct typographical errors in the DNA of cells.

The current most efficient method of doing genome editing is to design a nuclease, a protein, that will bind to a specific site in the DNA and break the DNA at that site. This activates the cell to try to fix the break, and the cell can try to fix this break in one of two ways.

One of the ways is to simply glue and stitch the ends back together. Now, this gluing process is mostly accurate, but occasionally it will create insertions and deletions at the site of the break, and this is a way of inactivating a harmful genetic element.

The other way that a cell can fix a double stranded break is what we call homology-directed repair, which is essentially, as has been described, a copy and paste mechanism in which a copy of an undamaged piece of DNA is made and then swapped in for the damaged piece of DNA. In this way, we can precisely change single letters of the DNA; we can change multiple letters of the DNA. Again, it is through homology-directed repair that we can correct typographical errors.

There are multiple different ways to create that initiating double stranded break, but the CRISPR/Cas9 technology has really revolutionized this field because, as has been mentioned, it is simple to use, it is highly active, and when used in a controlled fashion is highly specific.

While there are no clinical trials in the U.S. or Europe right now using the CRISPR/Cas9 technology for genome editing, I expect that in the next 12 to 18 months, there are going to be multiple such trials.

I want to discuss one example of how my lab is using the CRISPR/Cas9 technology, and that is to treat sickle cell anemia,

which we estimate affects about 100,000 people in the U.S. They all have mutations in the globin gene.

What we are able to do in the lab now is to use the CRISPR/Cas9 homology direct to repair pathways to correct around 50 to 70 percent of the cells, the blood stem cells, from patients who have this disease. It is estimated that if we can keep above 20 percent, that this would cure the disease.

In addition, the specificity is very high and we are about hundred to a thousandfold more specific than just cells living on their own without being exposed to genome editing.

We have now had very great conversations with the FDA about what our path from the lab to the clinic is, and we are hoping that we are able to bring this to clinical trails in 2019.

In the last few seconds, I want to just point out that we believe that the current regulatory structure with the FDA, the Recombinant DNA Advisory Committee, and the IRB is completely adequate in handling the assessment of the size and ethics of doing genome editing of somatic cells.

I hope that the controversial issues that surround genome editing do not distract us from being able to stay focused and committed to developing curative therapies for devastating genetic diseases like sickle cell anemia.

With that, I want to thank you and thank you for the invitation.

[The prepared statement of Dr. Porteus follows:]

PREPARED STATEMENT OF MATTHEW PORTEUS

The world is still troubled by diseases for which we have no cure. Some of the most devastating diseases for which we have no cure are monogenic diseases-disease's in which a child is born with an inherited mutation in a single gene causing a disease. Sickle cell disease, beta-thalassemia, cystic fibrosis, hemophilia, and Huntington's Disease are just a few of the most common and well known genetic diseases. It is estimated that there may be ~10,000 such diseases affecting a total of ~35 million people in the United States and >350 million people worldwide although the true health burden is unknown and could be much greater. These diseases not only have devastating impact on the patient, but incur great costs on families, communities, and societies. Most of these have no cures and finding such cures would have broad health and economic benefits. Gene therapy is one approach to finding cures and after 40 years of hard and focused work, gene therapy is beginning to pay off with hundreds of patients now having better lives because of it.

Genome editing is a more precise form of gene therapy and allows researchers to change the sequence of the DNA in a cell with single letter precision. It has generated tremendous excitement because it offers a conceptual approach to providing an ideal cure for thousands of diseases. While genome editing has been studied for >15 years, the pace of discovery has accelerated in the last 5 years with the development of new tools, most notably the CRISPR/Cas9 nuclease system. The CRISPR/Cas9 system allows scientists to correct disease-causing mutations in human cells with unprecedented efficiencies. In my lab, for example, we can correct the mutation that causes sickle cell disease in patient derived blood stem cells at a frequency of 50–80 percent. For severe combined immunodeficiency ("bubble boy disease") our correction frequency is 40–50 percent. For both the correction is highly specific and exceeds the level of correction by 5–10 fold over the efficiency that is predicted to be needed to cure a patient. We have been working closely with the FDA to bring these therapies to patients in the next 12–18 months.

We believe that the current regulatory structure has been appropriate as researchers begin to bring somatic cell editing for the treatment of disease to clinical trials and ultimately to market as an approved drug. The FDA has shown flexibility in working with researchers to expedite these therapies in a safe fashion to patients. Moving forward, as the research and medical community, private sector, and regulatory agencies, become more familiar with genome editing based therapeutics, we hope that the FDA will be flexible in its thinking such that cures can be brought

to market not just for diseases for which there is a solid commercial incentive but also for diseases that are not commercially profitable.

While the application of genome editing of somatic cells to cure disease is accelerating, there are a number of other applications of genome editing that have generated headlines and controversy. These other issues, should not distract from what is needed to bring curative somatic cell based therapies to patients——including sustained, substantial financial support, excellent public/private partnerships, and an active, scientifically based and flexible regulatory structure.

The other issues surrounding genome editing, which notably are not new and have been discussed and debated for decades in the scientific, medical, bio-ethical community, not to mention in movies and stories. These issues include the use of genome editing to: 1) Better understand early human development as a research tool; 2) Create genetic changes that would be passed along the germline; 3) Create so called genetic enhancements in humans. Broad, inclusive and continued discussions are needed in each of these areas. The use of genome editing as a research tool for understanding early human development will likely yield discoveries about what it means to be human and improve the current practice of in vitro fertilization. The potential use of germline/heritable editing to treat disease is likely to be quite limited; would be obviated by improvements in somatic cell genome editing or gene therapy; and reasonable and restrictive criteria by which it might explored have been outlined by the recent National Academy of Sciences/National Academy of Medicine International Study Committee entitled "Human Genome Editing: Science, Ethics and Governance." Finally, the use of genome editing or any other genetic means for "enhancement" violates multiple fundamental core beliefs of our society and other societies. The FDA currently has the authority to regulate such potential applications in the United States. Ongoing international conversations and meetings will be important to gain agreement trans-nationally on the issue of enhancement.

THE RELATIONSHIP OF GENETICS TO HUMAN DISEASE AND HUMAN TRAITS

The instructions or code for the actions of a cell are embedded in the DNA sequence of the cell's genome. DNA consists of a series of nucleotides (letters (A, C, G, T)) and it is the order of these four letters that the cell decodes. The primary unit of the genome is a gene which consists of two major parts: 1) The coding part of the gene gives instructions to the cell about how to make a protein (proteins are the machines that carry out the work of the cell) and 2) The non-coding part of the gene gives instructions as to when and where the cell should make the protein. A basic example of how a gene works is the human beta-globin gene (named HBB). The coding part of the HBB gene instructs the cell to make the beta-globin protein in a certain way. The beta-globin protein is an essential part of a complex that carries oxygen from the lungs to the tissues (such as brain, heart, muscles, intestines.). The non-coding part of the HBB gene instructs the cell when and where to make beta-globin protein. For the HBB gene, the instructions tell the cell to only make beta-globin protein in red blood cells but not in any other cell types, such as brain cells or even other blood cell types.

Every cell in a person has a DNA sequence that is nearly identical but not exactly identical to the sequence created when the sperm fertilized the egg and the sperm DNA combined with egg DNA to make the full DNA complement needed for a human cell to function. The sequencing of the human genome revealed that each cell has ~6 billion total nucleotides in the DNA (~3 billion from the egg and ?3 billion from the sperm). Except for the X chromosome and Y chromosome in males, every person has two copies of each gene.

Since DNA is a chemical, the nucleotides (letters) can be changed by exposure to other chemicals creating DNA variants (or "mutations"). This mutation process is ongoing and each day it is estimated that a cell acquires between 1–100 new mutations per day. Thus, every cell in the body has its own unique sequence of DNA. Moreover, cells often intentionally create changes in their DNA. In the development of the immune system, for example, the cells rearrange their genes ("VDJ recombination") that help fight infection in order to create a strong and robust immune system to deal with the world we face. In the development of sperm and egg (our germ cells), there is the regulated rearrangement of the DNA ("meiotic recombination") to intentionally create genetic diversity in the next generation.

There is tremendous variation between the DNA sequence of one individual and another, thus providing the basis for the rich variation and diversity that has been an important contributor to human success and robustness. Almost all of the key features that we ascribe to being human, however, are not encoded by a single gene but are shaped by a large network of genes interacting with the environment. We

have only rudimentary knowledge of these gene networks and environmental interactions and ongoing sustained and substantial funding for research is needed.

An inherited genetic disease ("monogenic disease") is caused when a person is born with a sequence in a gene (a mutation) such that the gene does not perform in a healthy way-either the gene is instructing the cell to make a protein that does not work properly or the gene instructions for telling the cell where and when to make the protein are off. Most monogenic diseases are caused by mutations that cause the gene to instruct the cell to make a disease-causing protein, rather than having the cell to make a functional protein in the wrong time and place. There are estimated to be 6,000–10,000 different genetic diseases. Sickle cell disease, cystic fibrosis, hemophilia, and Huntington's disease are all examples of monogenic diseases. All genetic diseases are classified as rare in the United States because they affect less than 300,000 people in the country it is estimated, for example, that 100,000 people in the U.S. have sickle cell disease, 30,000 have cystic fibrosis, and 30,000 have Huntington's Disease. Most genetic diseases are classified as ultra-orphan diseases because they might affect tens or less people in the U.S. at any one time point. While each genetic disease might not affect a lot of individuals, however, to the patients, families and communities they are devastating diseases that often have no cure or even good treatment to lessen the severity.

There are other diseases, such as cancer, that are acquired genetic diseases. In acquired genetic diseases, the DNA sequence of a cell changes after a birth and that cell now receives instructions that can cause disease. In cancer, a cell may acquire mutations that instruct the cell to make a variant of a normal protein or it may acquire mutations that instruct the cell to make a protein that it normally would not. Both types of mutations are usually present in cancer cells.

Finally, there is a fascinating interaction between the environment and our genes. Our DNA sequence may influence our health and who we are but it is not deterministic. Even in the most severe genetic diseases, such as sickle cell disease and Huntington's disease, there is tremendous variation in how the disease affects patients determined by the environment and not determined by the DNA sequence. An example is sickle cell disease, where every patient carries the same mutation. In the United States the average life span for sickle cell disease patients is the mid–40's whereas the average life span in Africa's 5–8 years of age. In this case, living in an environment where there is a sophisticated health care system dramatically alters the life of a patient.

While the sequence of the gene shapes when and how a gene will be expressed, so does the environment we live in. That is, signals from the environment also control when and where a gene is expressed, so again the DNA sequence of a genome is not deterministic.

The relationship of the environment with the genome also shows how there is no such thing as one "best" genome. Instead different DNA sequences may be better in one environmental situation but worse in others. One important example is the CCR5 gene, a gene that helps regulate how our immune system responds to infection. A small number of people have mutations in the CCR5 gene that make them resistant to infection by HIV. But these same people are more susceptible having severe infections when they get West Nile Virus or other infections. Thus, in an environment with high prevalence of HIV, it might be beneficial to have a CCR5 mutation. In an environment with a high prevalence of West Nile Virus, however, it would be a disadvantage. We usually do not know into what environment we are going to be born into or what environments we will end up in as we live our lives. I never expected in my lifetime to be testifying in front of the Senate HELP Committee, for example.

We are just beginning to understand the complex ways that the environment and genome interact and any predictions about how changing the DNA sequence of a healthy individual would impact the life of that individual should be taken with a large spoonful of humility.

In sum, for most people the DNA sequence of a person shapes but does not determine their health. For certain individuals with monogenic diseases, however, they had the unfortunate luck, through no fault of their own, to be born with a sequence in a gene that causes them to have a severe disease, usually a disease for which we currently have no cure or even treatment to lessen its severity. Finding transformative therapies, such as by using genome editing, is of tremendous importance.

GENOME EDITING IS A PRECISE FORM OF GENE THERAPY TO TREAT HUMAN DISEASE

Gene therapy is based on the idea that changing the DNA of a cell can be a way to cure diseases. Genome editing is a more precise form of gene therapy. Genome editing is the ability to change the sequence of the DNA of a cell with both spatial

and nucleotide precision. A list of changes that can be done using genome editing include, but are not limited to the following: 1) making precise mutations in genes in order to inactivate them; 2) deleting specific segments of DNA, 3) simply changing one letter/nucleotide of DNA to another or; 4) inserting large DNA segments into precise locations in the genome. Each of these uses of genome editing has potential applications in the treatment of human disease.

While there are ways of performing genome editing without making a specific DNA break, the current most efficient method of performing genome editing is to use a DNA double-strand break. In this method, a nuclease is designed to bind to a specific DNA sequence in the genome and after binding to cut both strands (thus creating a DNA double-strand break). The double-strand break then activates the cell's own machinery (a complex of proteins) to repair the break. It can repair the break in two primary ways.

1) In non-homologous end-joining (NHEJ) the cell glues/stitches the two-ends back together. Usually this stitching is accurate but sometimes there is a loss or gain of extra letters during the joining which then results in an INDEL (for insertion/deletion) mutation at a specific location in the genome. This NHEJ mediated genome editing usually results in a mutation-thereby inactivating or breaking the gene.

For example:

Original Sentence:	THISISAHARMFULGENETICSEQUENCE
Sequence after a break:	THISISAHARM/ /FULGENETICSEQUENCE
Sequence after NHEJ:	THISISAGENETICSEQUENCE

2) In homology directed repair (HDR) the cell finds a piece of DNA that is nearly identical to broken DNA, makes a copy of the undamaged DNA and then uses the new DNA to paste into the damaged site (cut, copy and paste).

For example:

Original sequence:	THISISASENTENCEWITHOUTAYPOGRAPHICALERROR
Sequence after a break:	THISISASENTENCEWITHOUTAYPOG/ /ARPHICALERROR
Copy of Undamaged DNA:	NTENCEWITHOUTATYPOGRAPHICALERR
Sequence Genome after HDR:	THISISASENTENCEWITHOUTATYPOGRAPHICALERROR

Using HDR mediated genome editing, therefore, one can create precise changes in the letters for the genomic DNA.

There are multiple different tools to design an engineered nuclease to make a specific DNA doublestrand break. These include homing endonucleases, zinc finger nucleases (ZFNs), TAL effector nucleases (TALENs), and RNA guided based nucleases including variations such as the CRISPR/Cas9 nuclease (please see briefing from ASGCT on November 21, 2016 for more details). There are likely going to be even more tools developed in the future. In the U.S. and Europe, all currently approved genome editing clinical trials use either ZFNs or TALENs-CRISPR/Cas9 based trials will likely begin in 2018 and 2019. Nonetheless, the CRISPR/Cas9 system is currently the best tool to perform genome editing because of its simplicity of design, its high activity, and when used carefully, its high specificity. The CRISPR/Cas9 tool has opened the field of genome editing to a much broader swath of investigator both in the US and around the world and as a consequence has transformed the field. With prior nuclease tools there was a substantial barrier to scientists entering the field because of a small number of gatekeepers who had the necessary expertise for that nuclease. With the simplicity of the CRISPR/Cas9 tool, the role of gatekeepers to using genome editing has essentially disappeared. While the use of CRISPR/Cas9 is not as simple as it is sometimes described (that it can be easily used to genetically engineer cells in a garage), it is a simple enough that a reasonably staffed and equipped lab can use the tool quite easily. The thousands of publications in the last 4 years from small and large institutions in the United States and across the world are an objective marker of the broad utility of CRISPR/Cas9 based genome editing. While CRISPR/Cas9 Therapeutic Applications of Genome Editing to Humans based genome editing can be easily used for research in the lab, translating its use to treat human disease remains a complex and sophisticated process that goes far beyond simply having expertise in the editing process itself.

For human therapeutic applications, the CRISPR/Cas9 tool does not enable theoretically applications that could not be done using other nuclease platforms. Prac-

tically, however, it makes such applications more feasible. My research program has used all of the above nuclease platforms over the last 15 years and currently uses the CRISPR/Cas9 tool because we have identified it as having the features that make translating genome editing to the cure or treatment of serious human diseases most feasible.

GENOME EDITING AS A RESEARCH TOOL

The CRISPR/Cas9 tool has enabled a broad range of researchers to use the powerful approach of genome editing as a research tool to gain better understanding of biomedical processes. This development has already resulted in important discoveries in all aspects of biomedical research including, but not limited to, cancer, infectious diseases, autoimmunity, neurodegenerative diseases, developmental diseases and monogenic disease. These applications are uncontroversial and with significant and sustained support from the Federal government will likely transform our understanding and treatment of disease both in the short term (next five years), medium-term (next 5–20 years) and long-term (over the next 20 years).

There are applications of genome editing, however, that require ongoing and further broad discussion. These applications of genome editing were possible using prior genome editing tools, but have become substantially more feasible with the discovery of the CRISPR/Cas9 tool.

One such application is the use of genome editing to better understand early human development. It is clear that early human development cannot be fully understood by studying the early development of other species, particularly mice. The precision of genome editing provides a powerful tool to better understand this critical stage in human development. From a research perspective, using genome editing of human zygotes (whether at the blastocyst stage from unused embryos derived from in vitro fertilization procedures or created directly for research purposes) will lead to important discoveries. There is a discrepancy across countries and across states within the United States about the legality and permissibility of such studies. It is possible that scientists who are interested in this stage in early human development will take their research programs to places where such research is more permissive. It is also important through public discussion and debate that shared beliefs are explored such that potential appropriate agreed upon limits and guidelines are generated.

A second area for further discussion is the use of genome editing to create large animal models of human disease. Using the new tools of genome editing it is now possible to create specific models of devastating human diseases in animal models other than mice. This will result in the intentional creation of suffering in these animals. There should be a forum that allows all interested parties to participate in adjudication of the moral, scientific and cultural risk/benefit of intentionally creating and propagating such non-rodent models. Whether that adjudication should be for non-human primates only or also include the creation of models in other species, such as dogs and pigs, needs to be broadly discussed.

GENOME EDITING OF SOMATIC CELLS TO TREAT OR PREVENT DISEASE

One of the areas that generates the most excitement for genome editing is its application to treat or prevent human disease. While exciting clinical successes have now been reported for the treatment of monogenic inherited diseases (severe combined immunodeficiency, Wiskot-Aldrich syndrome, metachromatic leukodystrophy, cerebral adrenoleukodystrophy, spinal muscular atrophy, hemophilia, beta-thalassemia, congenital blinding diseases.) and cancer (engineered Chimeric Antigen Receptor T-cells) using gene therapy, there remains tremendous excitement and potential for genome editing.

Genome editing can be roughly divided into ex vivo and in vivo approaches (nicely described in the November 21, 2016 briefing documents provided by the American Society of Gene and Cell Therapy to the HELP Committee). In ex vivo approaches, cells from a patient are removed from the body, genetically modified outside the body, and then transplanted back into the patient. In ex vivo gene therapy, the therapeutic product is a therapy that combines genome editing (using genome editing to modify the genomic DNA sequence of the cell) with cell therapy (transplanting the cells back into the patient). In in vivo genome editing, the genome editing machinery is packaged into a vector. The vector is then delivered directly to the patient with the intent of modifying the appropriate somatic cells of the body to achieve a therapeutic effect without unintentionally modifying the germline cells of the patient.

There are a broad number of diseases for which genome editing is being developed to treat. Some of these, such as sickle cell disease, severe combined immuno-

deficiency, beta-thalassemia, are best approached using an ex vivo strategy, while others, such as congenital blinding diseases and muscular dystrophies, are probably best approached using an in vivo strategy. For many diseases, more research needs to be done in order to determine whether an ex vivo or in vivo approach will give the best safety and efficacy.

In these approaches, genome editing is used to fundamentally correct a missing function. Another use of genome editing is to enhance the disease treating function of the cell. The enhancement of cell activity to treat disease should not be confounded with enhancement of traits in humans. An example of such an application is using genome editing to increase the safety and efficacy of CAR-T cells against not only leukemia but also against solid tumors, which so far have been recalcitrant to the activity of first generation CAR-T cells.

CRISPR/Cas9 based genome editing strategies to treat human disease, both genetic diseases and cancer, are likely to enter clinical trials in the United States in the next 1–2 years.

The current regulatory structure in the United States, which has been developed around the development of gene therapy, is well suited to assess which trials and products should be approved in the United States. While the field of therapeutic genome editing is relatively new, the FDA has the authority and expertise to make the appropriate judgments. For issues that may have broader issues, the Recombinant DNA Advisory Committee (RAC) has the authority to evaluate genome editing based clinical trials of somatic cells with public input and then providing advice on such trials. Finally, institutional IRBs have the authority and ability to engage relevant scientific and medical expertise as needed to evaluate risk/benefit and give ultimate approval to deliver the therapy as part of a clinical trial. ***This safety first, patient-centric regulatory structure does not need any major structural changes to handle the therapeutic application of genome editing of somatic cells.***

There are areas of regulation of somatic cell editing for disease that should be considered in order to enhance the distribution of this potentially transformative technology.

1) For first in human uses of genome editing, the current regulatory structure is appropriate. But if genome editing strategies are shown to be safe and are based on a shared platform, the regulatory agencies should have the flexibility to standardize a core set of experiments to allow investigators to bring transformative therapies in a more streamlined fashion to patients. In this way the financial resources of large pharmaceutical companies or well-funded biotechnology companies, whose fiduciary interests might not always align with a developing a therapy for a disease that affects only a small number of patients, would not be necessary. This regulatory flexibility would not preclude such companies from becoming involved in developing such therapies if they chose to, however.

2) The United States should consider developing a more flexible approval structure for cell and gene therapy products based on data from well-designed early clinical proof-of-concept clinical studies that show both safety and efficacy. This new flexible structure might be similar to what has been put in place in Japan or the pilot program at the European Medical Agency. In this structure, a conditional, time-limited approval for a product is given such that the company can generate revenues while definitive safety and efficacy data is generated. This flexibility would also facilitate the development of therapies for ultra-orphan diseases.

3) There may be certain devastating childhood diseases for which gene therapy and genome editing needs to be administered before birth to be effective. Depending on the situation and stage at which the therapy might be administered, there is a chance of the unintentional modification of cells that give rise to germ cells. The regulatory agencies should be given the flexibility to evaluate the risk/benefit of such a proposed therapy. They may need to be given the authority to evaluate the ethical risk/benefit in addition to the medical risk/benefit in certain circumstances.

In sum, the application of genome editing in somatic cells shows tremendous promise to provide cures for patients with diseases who currently often have no disease-modifying, much less curative, therapy available. While there is excellent support currently from a large variety of funding sources, the long-term success of the clinical applications of genome editing will still require the sustained and substantial financial support of basic science research-not only of the research itself but also of talented, creative, and motivated junior researchers who will discover therapies that we might not even be able to currently imagine. It should be noted for example, that the best genome editing tools we now have, were discovered from basic re-

search that at the time was seemingly unrelated to gene therapy, genome editing or developing transformative therapies for patients.

HERITABLE (GERMLINE) EDITING TO TREAT OR PREVENT DISEASE

As therapeutic cell gene therapy and genome editing becomes better and more efficient, the number of diseases for which it might not work, becomes smaller and smaller. The consequence of such improvements in somatic cell genome editing and gene therapy, is that the need for having to make genetic modifications in cells that would then be passed along to future generations will decrease.

Nonetheless, there still could be certain diseases for which somatic cell editing may not be possible or effective-such as for diseases in which the pathologic manifestations occur prior to birth and are not reversible.

In this situation, the only way to prevent or cure the disease may be to intervene at such a stage that genetic modification of cells to treat or prevent the disease will result in the genetic modification being passed along to future generations (heritable editing).

The recent International Committee on Human Gene Editing: Scientific Medical and Ethical Considerations sponsored by the National Academy of Sciences and National Academy of Medicine, released a report "Human Genome Editing: Science, Ethics and Governance" (hereafter called the "NAP Report" and accessible at: *https://www.nap.edu/catalog/24623/human-genome-editing-science-ethics-and-governance*). This Committee considered this possibility and outlined some very specific and relatively restrictive criteria by which one might consider such an approach (listed here):

- Absence of reasonable alternatives
- Restriction to preventing a serious disease or condition
- Restriction to editing genes that have been convincingly demonstrated to cause or to strongly predispose to the disease or condition
- Restriction to converting such genes to versions that are prevalent in the population and are known to be associated with ordinary health with little or no evidence of adverse effects
- Availability of credible pre-clinical and/or clinical data on risks and potential health benefits of the procedures
- Ongoing, rigorous oversight during clinical trials of the effects of the procedure on the health and safety of the research participants
- Comprehensive plans for long-term, multigenerational follow-up while still respecting personal autonomy
- Maximum transparency consistent with patient privacy
- Continued reassessment of both health and societal benefits and risks, with broad on-going participation and input by the public
- Reliable oversight mechanisms to prevent extension to uses other than preventing a serious disease or condition

All of these criteria are important and need continued and ongoing discussion. I will emphasize that the first criteria, "Absence of reasonable alternatives," is quite restrictive because In Vitro Fertilization followed by Pr Implantation Genetic Diagnosis (IVF–PGD) serves as an alternative to almost every situation that a couple might encounter if they desired to have a genetically related child without disease. The rare situations of both parents carrying an autosomal recessive disease, one parent having both copies of an autosomal dominant gene (such the child would have a 100 percent chance of inheriting one the disease causing dominant genes), or specific types of genetically based infertility are the few examples where IVF–PGD would not be an approach to having a genetically related child without disease. While the process of IVG–PGD remains quite inefficient, it is likely to improve with time (particularly as genome editing is used to further understand this stage of human development). There are strong arguments that IVF–PGD would reduce economic and healthy suffering costs for patients, parents, families, communities, and societies. In the United States the cost of IVF–GD is not covered by insurance, however, and thus is only available to people who have the resources to pay for it directly.

GENE THERAPY/GENOME EDITING FOR ENHANCEMENT

A long discussed potential application of genetic engineering, gene therapy, and now genome editing is for enhancement—the application of the procedure to genetically engineer humans who have characteristics beyond what they could achieve by hard work and careful living. I believe that such applications violate many of the key ethical and moral beliefs of our country and society. While we should endeavor to create a society in which everyone has the opportunity to achieve their goals, I

do not believe genetic tools should be used to do so. I believe that the goal of the biomedical research establishment is to create healthy babies/humans, not designer babies/humans. Using genetic methods to treat a patient to remove suffering and so that they can live in the normal range of humans is different than using genetic enhancement to give one person an advantage over another. The following are reasons for this assessment. For purposes of this document, I will use the term "genome editing" to encompass all such genetically based activities for the purpose of enhancement.

- Genome editing for enhancement involves treating people as objects, not as humans.
- Genome editing for enhancement reduces personal autonomy.
- Genome editing for enhancement violates the principle of humility.
- Genome editing for enhancement violates the principle that the human traits we consider most important are the result of the interaction of multiple gene variants and an environment and cannot be defined by a single gene or gene variant.
- Genome editing for enhancement increases the risk of structural inequality.
- Genome editing for enhancement increases the risk that we increase structural stratification with the belief that one human being is better than another.
- Genome editing for enhancement does not respect that engineering for one trait may result in compromising the long-term health of the individual.
- Genome editing for enhancement increases the risk that we make evaluations under the rubric that there is one best thing. There is no such thing as one best trait, human characteristic or feature.

The concerns listed are magnified if applied to heritable/germline genome editing.

The CHAIRMAN. Thank you, Dr. Porteus.

Ms. Bosley, welcome.

STATEMENT OF KATRINE BOSLEY

Ms. BOSLEY. Thank you.

Chairman Alexander, Ranking Member Murray, and Members of the Committee.

Thank you for the opportunity to testify today about genome editing technology.

I am Katrine Bosley, President and CEO of Editas Medicine and at Editas, we are committed to harnessing the power and potential of CRISPR genome editing to develop medicines for patients with serious diseases where other technologies have not been able to help.

Our company was founded 4 years ago in Cambridge, Massachusetts and we built a team of over 100 people to tackle these deep scientific challenges of turning this exciting science into medicines.

There are a few times in our lives when science astonishes us. When something was science fiction yesterday, but now is reality. This is one of those moments.

Our DNA is at the root of each one of us, that unique combination of genes that make you who you are. Sometimes, though, there are mistakes in DNA, mutations in genes that can cause many different kinds of serious diseases.

There are over 6,000 different genetically defined diseases and the National Organization for Rare Disorders says that 95 percent of them have no approved therapies.

What if you could address the root cause of these diseases driven by mutations in our DNA? What if you could repair the broken genes? How many patients could we help? This is the promise of genome editing.

We bear a great responsibility to patients, to their families, and to society broadly, and we take that responsibility very seriously.

CRISPR, which is an acronym for Clustered Regularly Interspaced Short Palindromic Repeats, refers to a recently developed genome editing technology that can revise, remove, or replace DNA. It is the latest in a series of genome editing technologies which includes zinc finger nucleases, TALEN's, and meganucleases.

At Editas Medicine, our most advanced CRISPR program is focused on a rare disease called Leber's Congenital Amaurosis type 10 or LCA 10. Children with LCA 10 go blind and they live with that condition the rest of their lives. There are no treatments today.

Our goal is to file an investigational new drug application with the FDA for this program by mid 2018. Our broader pipeline focuses on a range of other diseases including other eye diseases, inherited blood disorders such as sickle cell disease, and producing new cell therapies to treat cancer along with our partner Juno Therapeutics.

Editas Medicine and, to my knowledge, all the other companies working in this field are exclusively developing medicines that work by making non-heritable gene edits to somatic cells. This means that these non-heritable gene edits cannot be passed onto future generations.

In the United States, genome editing clinical trials are conducted under the current robust regulatory Federal framework. This framework has guided clinical research and drug development involving genetic technologies over the past 40 years.

Genomic medicines developed with novel genome editing technologies like CRISPR have and will be subject not only to FDA review, but also to public review by the NIH's Recombinant DNA Advisory Committee, or the RAC.

In conjunction with the RAC, the FDA is overseeing gene therapy development since the 1990's and these two agencies, working in tandem with other oversight mechanisms, will use the same framework to oversee clinical applications of CRISPR genome editing technology.

The United States has a rigorous, transparent, and flexible regulatory system that is pro-patient, pro-innovation, and has served as a model for the rest of the world.

Today's hearing is another hallmark in this Committee's long and distinguished history of overseeing biomedical research and promoting a tremendous American ecosystem of biomedical innovation and service of patients.

At Editas Medicine, we are fully aware that genome editing in general, and CRISPR in particular, is a fast moving, potentially disruptive technology. That is why we believe it is our responsibility to engage with major stakeholders in a highly transparent and respectful manner.

I know that the leading organizations in this area including BIO, ARM, and the American Society for Gene and Cell Therapy are also deeply committed to engaging with others on the science and policy implications of genome editing.

I have been in the biotech industry for more than 25 years and it is hard to compare genome editing with any other technology that I know. The pace of innovation, the profound potential to help

patients, the revolutionary impact on healthcare, all of this makes the field of genome editing truly exceptional.

Thank you for the opportunity to testify today and I look forward to your questions.

[The prepared statement of Ms. Bosley follows:]

PREPARED STATEMENT OF KATRINE BOSLEY

Chairman Alexander, Ranking Member Murray, and Members of the Committee, thank you for the opportunity to testify today about genome editing technology.

I am Katrine Bosley, CEO and President of Editas Medicine. At Editas Medicine, we are committed to harnessing the power and potential of CRISPR genome editing to develop medicines for patients with serious diseases where other technologies have not been able to help. We are only focused on applying our CRISPR genome editing platform to cells that cannot pass on changes to future generations. Our company was founded 4 years ago in Cambridge, Massachusetts, and we have built a team of over 100 people to tackle the deep scientific challenges of turning this exciting—but young—technology into medicines. We are one of a small number of companies in this field of genome editing, and we believe we are on the brink of a truly exciting new era of medicine, powered by genome editing technologies.

There are a few times in our lives when science astonishes us, when we are suddenly able to do something that seemed like science fiction just the day before. This is one of those moments. Our DNA is at the root of who each of us is—that unique combination of genes that makes you who you are. But sometimes there are mistakes in DNA—mutations in genes that can cause many different kinds of serious diseases. There are over 6,000 genetically defined diseases, and, according to the National Organization for Rare Disorders (NORD), 95 percent of them have no approved medicines. What if you could repair broken genes? What if you could address the root of diseases caused by mutations in DNA? How many patients could we help in the years ahead? This is the promise and possibility of gene editing.

My testimony today will focus on how innovative American researchers, universities, and companies are advancing new genome editing tools like CRISPR to translate the value of the Human Genome Project and its insights into a new class of transformative medicines that work at the level of the gene to treat serious diseases that afflict millions of Americans. The field of gene therapy and genomic medicine has been working toward this moment for decades, and this year marks the first time that some of these patients will have access to gene therapy products approved by the U.S. Food and Drug Administration (FDA). These gene therapy product approvals promise to be the first of many new genomic medicines that can address previously untreatable diseases and help patients move from chronic to durable treatments. Continued success in this field will depend in part upon Congress maintaining the robust, but flexible regulatory system over novel genetic technologies that has operated effectively since the first recombinant genetic research began over 40 years ago. Maintaining regulation that is both rigorous and science-driven not only protects patients, it also helps the American biotechnology industry flourish. Our industry leads the world by a very long measure, and sophisticated, highly engaged regulators are a key and valued partner in this continuing success story.

At the outset, I want to remark that at Editas Medicine 1 we are fully aware that genome editing in general, and CRISPR in particular, represents a fast-moving, potentially disruptive technology that often evokes great hopes and, at times, legitimate concerns. That is why we believe it is part of our mission and responsibility to engage with major stakeholders in a highly transparent and respectful manner. Our company, and many of our partners and collaborators in medicine and industry, applaud the Committee for convening this hearing and judiciously engaging in the science and policy implications of genome editing.

I understand that the Committee also convened a bipartisan staff briefing approximately a year ago with the American Society of Gene & Cell Therapy (ASGCT), and, therefore, has already benefited from the insights of some of the world's leading genome editing experts. Today's hearing is another hallmark in this Committee's long and distinguished history of overseeing biomedical research and promoting the now-flourishing American biotechnology industry. From balanced oversight hearings of recombinant DNA technology in the 1970's to funding of the National Institutes of Health (NIH), overseeing and strengthening the FDA to last year's enactment of the 21st Century Cures Act, on a bipartisan basis you have thoughtfully helped develop a tremendous American ecosystem of innovation in service of patients. These forward-looking, bipartisan policies are now bringing forth unprece-

dented medicines that can transform, and often save, countless lives. For these reasons, I would like to thank the Committee for its historic and ongoing support.

This continued support will also be critically important for the United States to remain the global biotechnology leader and a beacon of hope for patients around the world. As the Committee is aware, developing medicines is a long, complex process that is riddled with setbacks and failure. At Editas Medicine, for example, we are a 4-year old company with no approved products to generate operating revenue. To date, we have raised approximately $500 million from investors and partners to fund our scientific discovery and clinical development of new medicines. We will need to raise significantly more capital before our first product is approved in the U.S. or Europe. This is a necessary and important undertaking for us to be successful in our ambitious goal to create these unprecedented medicines. We know how important this is—every week we receive letters and emails from patients and their families asking about our progress, and letting us know that they are paying close attention to everything we do. Patients are our motivation every day for discovering and developing CRISPR medicines.

I. What is Genome Editing?

In the world of medicine, the idea and the promise of genome editing is straightforward: *What if we could repair broken genes*? Our bodies depend on many intricate biological systems that follow instructions embedded within our genes. Even one mutation, which is a naturally occurring change in our DNA that disrupts the function of a gene, can result in serious or life threatening diseases. Most diseases caused by genetic mutations have no approved therapeutic options. Some of these diseases are well known: rare forms of blindness, sickle cell disease, cystic fibrosis, Huntington's disease, and hemophilia. Our goal in advancing genome editing is to repair these broken genes at the level of DNA.

CRISPR (pronounced "crisper") is an acronym for "Clustered, Regularly Interspaced, Short Palindromic Repeats," and refers to a recently developed genome editing technology that can revise, remove, and replace DNA. It is the latest in a series of genome editing technologies that can engineer molecules to cut DNA in a highly targeted manner, including zinc finger nucleases (ZFNs), transcription activator-like effector nucleases (TALENs), and meganucleases.

Beyond human health, genome editing can be applied to animal and plant DNA, as well as many organisms that are used in basic biological research. Applications in agriculture and animal health have the potential to deliver major advances to help feed the world. In basic research laboratories, the use of CRISPR technology is nearly ubiquitous. It is opening up a wide range of new ways to ask and answer essential biological questions. Researchers are using it to probe the internal workings of cells, to identify the actions of genes with unknown function, and to rapidly create new animal models of disease to enable testing and advancements of medicines of all kinds. Creative new applications of the technology keep emerging, and we are just at the beginning of seeing what can be achieved.

II. Innovative Researchers, Clinicians, and Companies Are Applying Genome Editing in Drug Development Programs to Meet Unmet Medical Needs of American Patients with Serious and Life-Threatening Diseases.

Mr. Chairman, it is simply impossible to overstate the needs of millions of American patients and their families who urgently need medical progress, treatments, and, wherever possible, cures. As we continue working to develop gene editing medicines to address this need, we are often asked what these medicines might look like. Genome editing medicines can take different forms, depending on what tissue in the body needs to be treated for a given disease. In some instances, the genome editing product could be administered directly to a patient. In these cases it could be a biological preparation (such as a viral or nanoparticle preparation to deliver the genome editing molecules) or edited cells (such as induced pluripotent stem cells, or iPSCs). The patient would receive the biological preparation or the cells as an injection, either systemically or to a specific tissue. In other instances, gene editing can be performed outside the body on a patient's cells—for example, cells from the blood like T cells. In these cases, a patient's cells would be removed, then edited, and then given back to the patient via an infusion.

Editas Medicine is working to deliver new genomic medicines that realize the potential of CRISPR genome editing. Our most advanced program is focused on a rare disease called Leber's Congenital Amaurosis Type 10 (LCA10). This disease afflicts children with significant vision loss and blindness. We have initiated a natural history study in LCA10 to better understand the disease's progression and intend to use the insights learned from this study to inform clinical trials for our first product

candidate in development, which is called EDIT–101. We aim to file an Investigational New Drug application with the FDA for this program by mid——Our broader pipeline focuses on genetically defined eye diseases, inherited blood disorders, and producing new cell therapies in immuno-oncology, along with our partner, Juno Therapeutics.

In addition to Editas Medicine, there are several leading biotechnology companies working to translate the promise of genome editing into medicines to help patients in need. These include CRISPR Therapeutics and Intellia Therapeutics, both of whom work on CRISPR technology, as well as bluebird bio, Cellectis, and Sangamo Therapeutics, who are pursuing drug development using other genome editing platforms. Editas Medicine and, to my knowledge, all of these companies are only focused on applying their technologies to cells that cannot pass on genetic information or any edits to future generations. As such, the editing is *non-heritable*, and only applied to somatic cells or cells that are derived from somatic cells.

Around the world, clinical trials with genome editing technologies are already underway in patients. Sangamo Therapeutics and Cellectis are two examples of companies whose ZFNs and TALENs-based genome editing products are currently in clinical trials. Last October, Chinese researchers were the first to inject a patient with CRISPR-edited cells in a clinical trial for lung cancer treatment. The CRISPR genome editing platform has yet to be used in a clinical trial in the United States or Europe, but U.S. companies are expected to initiate clinical trials soon.

III. Genome Editing to Treat Disease Falls Under a Robust and Comprehensive Regulatory System.

Those clinical trials are carefully regulated by Federal authorities. In September, FDA Commissioner Scott Gottlieb spoke to our common goals for intelligent oversight of the promising field of genome editing. He said, ".our principles for regulation allow and facilitate beneficial new innovation while making sure that FDA continues to meet its gold standard for safety and effectiveness."

Mr. Chairman, I believe this is an accurate description of the current, robust Federal regulatory framework that has guided clinical research and drug development involving recombinant genetic technology over the past 40 years. Genomic medicines developed with novel genome editing platforms like CRISPR have and will be subject not only to FDA review, but also public review by the NIH's Recombinant DNA Advisory Committee (RAC). The NIH's RAC dates back to the 1970's, and has afforded the American public with unique opportunities to review and comment on clinical trials and other information that would otherwise be deemed confidential by the FDA in its own, parallel review. This is appropriate for such novel technologies, and it has proven to be a strength of our existing regulatory framework. In conjunction with the NIH RAC, the FDA has overseen gene therapy development since the 1990's, and together, the two agencies will use this same framework to oversee potential clinical applications of genome editing technology, including CRISPR, to treat human disease. With these agencies working in tandem with Public Advisory Committees, local Institutional Review Boards (IRBs), and other oversight mechanisms, the United States possesses a rigorous, transparent, and flexible regulatory system that is pro-patient, pro-innovation, and has served as a model for the rest of the world.

As you know, the FDA has broad authority to uphold high standards of safety and effectiveness for any novel biological product, including genomic medicines. They have also had extraordinary success implementing a range of programs for collaboration with sponsors and expedited reviews, including the orphan drug, fast track, breakthrough therapy, priority review, accelerated approval, and the recently enacted Regenerative Medicine Advanced Therapy (RMAT) programs—all of which could expedite the availability of genomic medicines. Perhaps most importantly, in our experience, the Agency's leaders and scientific reviewers have also demonstrated a strong commitment to understanding the latest breakthroughs and to improving their regulatory science. I commend the FDA in particular for their outreach to leading academic and industry experts in genome editing. To date, the Agency has been forward-looking and thoughtful in starting early conversations about how they plan to integrate oversight of genome editing into their existing regulatory framework. As the field of genome editing continues to advance in the years ahead, these kinds of early, constructive, and collaborative engagements will be invaluable in keeping all parties aligned and focused on delivering important medicines to patients.

The European Union has also sought to understand and appropriately regulate this work. On October 18, the European Medicines Agency (EMA) gathered leading academics and companies together for an initial discussion around the oversight of clinical uses of genome editing. I attended this meeting, and the discussion focused used on their regulatory framework for gene therapies, how their Committee on Ad-

vanced Therapies (CAT) should think of genome editing medicines and setting standards under such a framework, and their appreciation of the importance of the EMA's regulatory science co-evolving with emerging technologies. While the EMA has demonstrated foresight on genome editing, it was my impression that the early engagement efforts of the FDA have brought the Agency to a closer familiarity with the leading edge of the field's rapid innovation. Like the FDA, the EMA is committed to learning and engaging with leading companies and researchers.

Our expectations for how genome editing medicines will be regulated are informed by the experience in the United States and Europe with genomic medicines technologies overall, including many years overseeing gene therapy clinical trials. In recent years, companies developing other genome editing technologies have initiated early clinical trials in the U.S. following reviews by the NIH RAC and the FDA.

IV. Recent NAS/NAM Report Endorses Existing Comprehensive Regulatory System.

We are fortunate to have authoritative, independent confirmation that genome editing will be carefully regulated under current law. In December 2015, the National Academies of Science and Medicine (NAS/NAM or Academies) co-hosted an international summit on human genome editing with the British Royal Society and the Chinese Academies of Science. The Academies spent 3 days exploring the scientific, social, and legal implications of genome editing, and offered a preliminary conclusion that clinical use of genome editing in somatic cells "can be appropriately and rigorously evaluated within existing and evolving regulatory frameworks. . ."

In February 2017, the Academies issued a comprehensive report titled "Human Genome Editing: Science, Ethics, and Governance." Mr. Chairman, I encourage the Members and Staff of this Committee to review its analyses and its specific, actionable recommendations to rely on current regulations to facilitate progress. Critically, the report reaffirms that "clinical trials of genome editing in somatic cells for the treatment or prevention of disease or disability should continue, subject to the ethical norms and regulatory frameworks that have been developed for existing somatic gene therapy research and clinical use to treat or prevent disease and disability."

We agree strongly with this conclusion and the finding that the Federal Government should continue to "use existing regulatory processes for human gene therapy to oversee somatic human genome editing research and uses." In short, the Academies' report confirms that current, multilateral Federal safeguards, standards, and oversight mechanisms, as well as long standing guidelines in the research community, preclude the need for additional, potentially disruptive restrictions of genome editing research.

V. U.S. Companies Are Developing Non-Heritable, Somatic Cell Medicines, and Not Germline Modifications.

As I mentioned, U.S. companies are exclusively developing *non-heritable* gene edits to somatic cells, which cannot pass on their genetic information to future generations. Editas Medicine is not working on editing germline cells, and we have no plans to do so. Nevertheless, the NAS February 2017 report raised the prospects of 1 day permitting germline editing for clinical application if select criteria could be met. Though this topic is beyond my scope and expertise, I would like to share two thoughts. The first is that edited human cells of all kinds are under the FDA's jurisdiction, and provisions in the Consolidated Appropriations Act of 2017 and the Consolidated Appropriations Act of 2016 effectively bar the Agency from allowing clinical trials of products that cause germline modifications.

Second, that the Biotechnology Innovation Organization (BIO) recently issued a position statement that reflects its member company consensus on germline editing for clinical application:

> BIO views the science of germline genome editing as having not advanced sufficiently for clinical applications to be appropriate at this time. As scientific developments progress, BIO urges continued discussion and engagement on this topic with important stakeholders, including Members of the patient, caregiver, regulatory, legal, academic, ethical, and faith communities, to determine if and under which conditions this status quo should be changed.

VI. Conclusion

Mr. Chairman, we are discussing this revolutionary translation of fundamental breakthroughs in the understanding of human genetics into innovative medicines thanks in great measure to the bipartisan commitment of Congress, including this Committee, and of successive administrations to fully fund the Human Genome Project. That historic achievement, in turn, would have been impossible without our country's extraordinary, decades-long commitment to basic research—a commitment

that built a system of higher education that leads the world and is the envy of other nations; that secured a lion's share of Nobel Prizes and patents in the sciences and medicine; and that has created breakthroughs in high technology, computation, the Internet, and medicine.

To sustain this extraordinary success, I urge the Committee to continue its support of robust research funding through NIH; to maintain its oversight of the FDA and support the Agency in its embrace of fast-moving scientific developments, including advances in genome editing; and, critically, to continue to support public dialog about the tremendous promise and important challenges in the field of genome editing. I am greatly encouraged that this hearing exemplifies the National Academies' recommendation that "[p]ublic participation. . . be incorporated into the policymaking process for human genome editing."

Dr. Gottlieb recently said that this field holds "the promise of changing the contours of human illness and altering the trajectory of medicine and science"—what the late Chairman of this Committee, Senator Kennedy, once called "the century of life sciences." I have been in this industry for more than 25 years. I can say without equivocation that it is hard to compare genome editing to any other field that I know. The implications for medicine and for patients who have as yet untreatable diseases; the scientific intensity as we work to overcome challenges translating the science into medicines; and the intensity of the public spotlight, given the profound implications of this technology, all make this field exceptional. We bear great responsibility to patients, to their families, and to society broadly. We take that very seriously. We are here for the long term, and want to listen and respectfully engage with all major stakeholders.

Thank you for the opportunity to testify today. I look forward to answering your questions.

SUMMARY

Chairman Alexander, Ranking Member Murray, and Members of the Committee, thank you for the opportunity to testify today about genome editing technology.

At Editas Medicine, we are committed to harnessing the power and potential of genome editing to develop medicines for patients with serious or life-threatening diseases. Our company was founded four years ago in Cambridge, Massachusetts, and we have built a team of over 100 people to tackle the deep scientific challenges of turning this exciting technology into medicines.

There are a few times in our lives when science astonishes us, when we are suddenly able to do something that seemed like science fiction just the day before. This is one of those moments. Our DNA is at the root of who each of us is—that unique combination of genes that makes you who you are. But sometimes there are mistakes in DNA—mutations in genes that can cause many different kinds of serious diseases. There are over 6,000 genetically defined diseases, and, according to the National Organization for Rare Disorders (NORD), 95 percent of them have no approved medicines.

CRISPR is an acronym for "Clustered, Regularly Interspaced, Short Palindromic Repeats," and refers to a recently developed genome editing technology that can revise, remove, and replace DNA. It is the latest in a series of genome editing technologies that can engineer molecules to cut DNA in a highly targeted manner, including zinc finger nucleases (ZFNs), transcription activator-like effector nucleases (TALENs), and meganucleases.

Editas Medicine is working to deliver new genomic medicines that realize the potential of CRISPR genome editing. Our most advanced program is focused on a rare disease called Leber's Congenital Amaurosis Type 10 (LCA10). This disease afflicts children with significant vision loss and blindness. We aim to file an Investigational New Drug application for this program by mid–2018. Our broader pipeline focuses on genetically defined eye diseases, inherited blood disorders, and producing new cell therapies in immuno-oncology, along with our partner, Juno Therapeutics. Editas Medicine is exclusively developing non-heritable gene edits to somatic cells, which cannot pass on their genetic information to future generations.

Genomic medicines have and will be subject not only to FDA review, but also public review by the NIH's Recombinant DNA Advisory Committee (RAC). In conjunction with the NIH RAC, the FDA has overseen gene therapy development since the 1990's, and together, the two agencies will use this same framework to oversee potential clinical applications of genome editing technology, including CRISPR, to treat human disease. With Federal agencies working in tandem with Public Advisory Committees, local Institutional Review Boards (IRBs), and other oversight mechanisms, the United States possesses a rigorous, transparent, and flexible regu-

latory system that is pro-patient, pro-innovation, and has served as a model for the rest of the world. While clinical trials with CRISPR editing have not yet entered clinical trials in the U.S., ZFN and TALEN-based genome editing technologies have already entered the clinic.

Many things make the field of genome editing exceptional: its scientific promise and intensity, its implications for medicine, and its potential to change the lives of patients living with serious or life-threatening diseases. We bear great responsibility to patients, their families, and to society as a whole. We take this seriously, and are committed to listening and engaging with all major stakeholders in a thoughtful and responsible manner.

Thank you for the opportunity to testify today. I look forward to answering your questions.

The CHAIRMAN. Thank you, Ms. Bosley.

Dr. Kahn, welcome.

STATEMENT OF JEFFREY KAHN

Dr. KAHN. Thank you.

Thank you, Chairman Alexander, Ranking Member Murray, Committee Members, and staff for the opportunity to offer testimony on this timely and vitally important subject today.

I am Director of the Johns Hopkins Berman Institute of Bioethics in Baltimore, where I also hold an endowed professorship in bioethics and public policy. As you heard in Senator Alexander's introduction, I was also a member of the National Academy of Sciences International Consensus Committee on Human Genome Editing.

I will focus my comments today on three topic areas, policy, history, and related areas of science and biomedical research to the topic today; existing ethical frameworks and oversight that apply; and ethical issues raised by the use of gene editing technologies in humans and considerations for future oversight of them.

The relevant policy history started in 1975 with the Asilomar Conference on Recombinant DNA Molecules. The summary statement focused on containment of the risks of creating and working with genetically modified organisms, and with the admonition to avoid experiments that pose, and here is a quote, "Such serious dangers that their performance should not be undertaken at this time," along with a call for continuing reassessment of issues arising in light of new knowledge gained with experience with the then-new genetic technology.

These voluntary suggestions gave way to more robust oversight as use of genetic technologies became more refined and with initial attempts to treat diseases in humans, with the now longstanding body that you have heard about three times now, the NIH Recombinant DNA Advisory Committee or RAC, which is charged with the review of proposed gene transfer research involving humans.

Ethical concerns in genetic modification in humans have been addressed through a range of policy and oversight approaches in order to limit certain types of research or to provide prospective oversight prior to particular proposals being undertaken.

There are a number of institution-level oversight mechanisms that will apply to gene editing research. While there is no single Institution-Level Committee that is currently responsible for gene editing research, there is robust oversight with some combination of Committees responsible for oversight depending on the specifics

of the research proposed. They include Institutional Bio-safety Committees; Institutional Stem Cell Research Oversight Committees, and institutional review boards which, of course, are charged with prospective review of all research involving humans.

In addition to institutional oversight requirements, there are regulatory bodies with roles that are relevant to gene editing research. The aforementioned RAC is charged with making recommendations to the NIH Director, here is a quote again, "On matters related to the conduct and oversight of research involving recombinant DNA."

I think it is clear that there is every indication that applications of gene editing tools, when they are applied to humans, will be subject to such oversight and review as well.

FDA review and approval would also be required prior to the administration of gene editing techniques in humans, a process that, in the case of gene transfer, takes place in parallel with, and informed by, the review process of the RAC.

There is a range of ethical issues posed by gene editing and related technologies for modifying human DNA, and today I will focus on just three.

First, the expanded use of therapies beyond indications on which any approvals might be based.

Second, interventions that might result in heritable genetic modification, sometimes called germline modification.

Third, some challenges that genome editing poses for regulatory oversight.

The first concern is related to the use of somatic gene editing approaches that have clear therapeutic application being used for other indications, including moving beyond therapies or preventive uses, and instead enhancement beyond what we might think of as normal abilities, a challenge long known within the gene therapy oversight process and effectively blunted through very limited clinical trials and strict processes of who should be included.

But as applications begin to make their way into the market, we will need to figure out how to prevent indication creep, as it is called, for uses that are unintended in terms of indications of approval.

The second concern has been the focus of much ethical analysis in the application of manipulation of genetic information in humans, and that is the potential to introduce changes that affect the germline.

The basis of this concern relates to the uncertainty of the effects of genetic modification, the ability to undo unintended changes, and the risks of passing on such unintended changes to future generations.

The NAS Committee that has been mentioned now noted that improvements in genome editing techniques are driving increases in the efficiency and accuracy of genome editing while also decreasing the risk of off-target events.

Because germline genome edits would be heritable, however, their effects could be multigenerational. As a result, both the potential benefits and the potential harms could be multiplied. We will need very strict oversight if that is ever to go forward.

Third, while oversight existing is robust and has proven to be effective at governing areas like gene therapy, there are ethical

issues described thus far, along with others, must be addressed in policy as gene editing tools become more widely used.

I will say, at the same time, prohibitions should not be the logical conclusion of addressing areas that require attention. We need only to look at two of our closest allies for a real world comparison of two policy approaches and how different approaches will have very different effects. I can speak more in questions, if you like. There are examples in Canada and in the U.K., which have taken very different approaches.

Let me just conclude by saying the U.S. has long played a leadership role in both science and in the responsible uses of the advances created by scientific discovery. We must be very careful to reflect the input and create pathways with appropriate oversight and appropriate public input. Only then, will we achieve a robust and credible policy framework that will assure the promise of responsible use of these technologies, while achieving their benefits for advancing scientific knowledge and human health.

Thank you.

[The prepared statement of Dr. Kahn follows:]

PREPARED STATEMENT OF JEFFREY KAHN

Chairman Alexander and Ranking Member Murray, thank you for the opportunity to submit testimony on this timely and vitally important subject.

I am Director of the Johns Hopkins Berman Institute of Bioethics in Baltimore, where I also hold an endowed professorship in bioethics and public policy. Relevant to my comments today I was a member of the National Academy of Sciences International Consensus Committee on Human Genome Editing.

I will focus my comments today on three topics: (1) policy history in related areas of science and biomedical research; (2) existing ethical frameworks and oversight; and (3) ethical issues raised by the use of gene editing technologies in humans and considerations for future oversight.

Related policy history

The relevant policy history started in 1975 with the Asilomar Conference on Recombinant DNA Molecules, whose summary statement focused on containment of the risks of creating and working with genetically modified organisms, and with the admonition to avoid experiments that pose "such serious dangers that their performance should not be undertaken at this time" along with a call for continuing reassessment of issues arising in light of new knowledge gained with experience with the then-new genetic technology. These voluntary suggestions gave way to more robust oversight as use of genetic technologies became more refined and with initial attempts to treat diseases in humans, with a now longstanding body called the NIH Recombinant DNA Advisory Committee or RAC charged with review of proposed gene transfer research involving humans.

Existing ethical frameworks and oversight

Ethical concerns in genetic modification in humans have been addressed through a range of policy and oversight approaches, in order to limit certain types of research or to provide prospective oversight prior to particular proposals being undertaken.

Institutional Oversight

There are a number of institution-level oversight mechanisms that will apply to gene editing research. While there is no single Institution-level Committee that is currently responsible for gene editing research, there is robust oversight with some combination of Committees responsible for oversight depending on the specifics of the research proposed. Those include:

Institutional Biosafety Committees (IBCs), charged oversight of research with recombinant or synthetic nucleic acid molecules;

Institutional Stem Cell Research Oversight Committees (SCROs), charged with institutional and ethical oversight of research on human embryonic stem cells and related areas of research.

While specifics of gene editing research will determine which if any of these existing institutional oversight mechanisms will apply, any research involving human participants must be also be reviewed and approved by Institutional Review Boards, charged with prospective review of all research involving humans, requiring appropriate risk-benefit balancing, informed consent of subjects, and monitoring adverse events that occur, in order to protect the rights and interests of those participating in research.

Regulatory Oversight

In addition to institutional oversight requirements there are regulatory bodies with roles that are relevant to gene editing research. The aforementioned NIH Recombinant DNA Advisory Committee (RAC) is charged with making recommendations to the NIH Director "on matters related to the conduct and oversight of research involving recombinant DNA."[1] In addition, the NIH Guidelines currently State that "RAC will not at present entertain proposals for germ line alterations."[2] This indicates a current effective prohibition on the use of germline modifying technologies for areas of research within the purview of the RAC, with every indication that applications of gene editing tools to humans will be subject to such oversight and review.

FDA review and approval would also be required prior to the administration of gene editing techniques in humans, a process that in the case of gene transfer takes place in parallel with and informed by the review process of the RAC.

Ethical Issues Raised by the Use of Gene Editing Technologies in Humans and Considerations for Future Oversight

There are a range of ethical issues posed by gene editing and related technologies for modifying human DNA, and I will focus on just three in my testimony today: (1) the expanded use of therapies beyond indications on which any approvals might be based; (2) interventions that result in heritable genetic modification; and (3) some challenges that genome-editing poses for regulatory oversight.

The first concern is related to the use of somatic gene-editing approaches that have clear therapeutic applications being used for other indications, including moving beyond therapies or preventive uses, and instead for enhancement beyond "normal" abilities, a challenge long known within the gene therapy oversight process and effectively blunted through very limited clinical trials with inclusion criteria for research participants. But as applications begin to make their way into the market, FDA will need to evaluate and apply its regulatory tools to assure that what has been termed "indication creep" or uses for what are unintended indications can be prevented or at least limited.

The second concern has been the focus of much ethical analysis in the application of manipulation of genetic information in humans, and that is the potential to introduce changes that affect the germline. The basis of this concern relates to the uncertainty of the effects of genetic modification, the inability to "undo" unintended genetic changes, and the risks of passing on such unintended changes to future generations. As the NAS International Consensus Committee noted, "improvements in genome-editing techniques are driving increases in the efficiency and accuracy of genome editing while also decreasing the risk of off-target events. Because germline genome edits would be heritable, however, their effects could be multigenerational. As a result, both the potential benefits and the potential harms could be multiplied."[3]

While acknowledging these concerns, if and when such technologies have developed sufficiently, policy decisions must be made that balance the individual-level benefits of using gene editing against societal-level risks. The NAS Committee recognized and analyzed this balancing and made recommendations about when if ever a clinical trial employing heritable genome editing could be acceptable, setting a very high bar-some have said with criteria that would be impossible to meet. I think the criteria are appropriately restrictive, and if they cannot be met, then such applications of gene editing tools would and should not be permissible.

Third, while existing oversight is robust and has proven effective at governing areas like gene therapy, the two ethical issues I've described thus far, along with others, must be addressed in policy as gene editing tools become more widely used. At the same time, prohibitions should not be the logical conclusion of addressing areas that require attention. We need only look to two of our closest allies for real-

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[1] Charter, NIH Recombinant DNA Advisory Committee, June 30, 2013.
[2] NIH Guidelines, Nov. 2012, Appendix M.
[3] *Human Genome Editing: Science, Ethics, and Governance*, National Academies Press, 2017, pp. 111-112.

world comparison of two policy approaches and how differences in regulatory approach will have very different effects. Just last week in Canada, a major group of researchers called for change to their Federal law that makes it a criminal offense with penalties of up to 10 years in prison for using gene-editing tools on cells that could lead to heritable genetic change in humans. The concern expressed by the group is that research has been stopped in ways that mean Canadian scientists are falling behind their international colleagues.

The counterexample is the United Kingdom, where scientists are taking the lead internationally in research involving potential human applications of these technologies. This owes not to lax oversight but rather the contrary—strict oversight with clear pathways for licensure by the responsible regulatory agency, allowing careful and controlled progress with clear reporting and evaluation of results before proceeding, creating a clear path forward.

There is no comprehensive regulatory approach, however, the absence of which creates an opportunity for some jurisdictions to craft lenient or nonexistent regulation, leading to the emergence of so-called "regulatory havens," the encouragement of both scientific flight and medical tourism, and more near-term concerns around scientific leadership and competitiveness, and a loss of ability to control research that is outside of U.S. jurisdiction.

In conclusion, the United States has long played a leadership role in both science and in the responsible use of the advances created by scientific discovery. This was certainly the case with the introduction of recombinant DNA technologies in the 1970's and it is critical that we continue to do so as the new and powerful genetic technologies become both more precise and more widely available. Existing oversight approaches are appropriate for providing part of a framework for addressing many of the issues raised by gene editing technologies. However, some areas require additional clarification or refinement, and my caution is that they not be addressed through additional bans or prohibitions. Instead work must be done to (1) identify gaps or areas requiring updated approaches to oversight in both in the near and longer terms, and (2) craft appropriate guidelines to address the areas identified, in order to create pathways to allow innovative science to go forward carefully and responsibly, and with appropriate oversight. This work must reflect input and contributions from the scientific community, ethics experts, policymakers, and a range of public stakeholders. Only then will we achieve a robust and credible policy framework that will assure the responsible use of these technologies while achieving their promise for advancing scientific knowledge and human health.

Thank you.

SUMMARY

I will focus my comments today on three topics: (1) policy history in related areas of science and biomedical research; (2) existing ethical frameworks and oversight; and (3) ethical issues raised by the use of gene editing technologies in humans and considerations for future oversight.

The relevant policy history started in 1975 with the Asilomar Conference on Recombinant DNA Molecules. These voluntary suggestions gave way to more robust oversight as use of genetic technologies became more refined and with initial attempts to treat diseases in humans, with a now longstanding body called the NIH Recombinant DNA Advisory Committee or RAC charged with review of proposed gene transfer research involving humans.

Ethical concerns in genetic modification in humans have been addressed through a range of policy and oversight approaches, in order to limit certain types of research or to provide prospective oversight prior to particular proposals being undertaken.

In addition to institutional oversight requirements there are regulatory bodies with roles that are relevant to gene editing research. The aforementioned NIH Recombinant DNA Advisory Committee (RAC), along with FDA review and approval would also be required prior to the administration of gene editing techniques in humans.

There is no comprehensive regulatory approach, however, the absence of which creates an opportunity for some jurisdictions to craft lenient or nonexistent regulation, leading to the emergence of so-called "regulatory havens," the encouragement of medical tourism, and more near-term concerns around scientific leadership and competitiveness.

Existing oversight approaches are appropriate for providing part of a framework for addressing many of the issues raised by gene editing technologies. However,

some areas require additional clarification or refinement, and my caution is that they not be addressed through additional bans or prohibitions.

The CHAIRMAN. Thank you, Dr. Kahn.

We will now go to a round of 5 minute questions. We will begin with Senator Collins.

STATEMENT OF SENATOR COLLINS

Senator COLLINS. Thank you very much, Mr. Chairman.

Dr. Kahn, the panel today has described gene editing technology that is so exciting as we think about conditions such as Duchenne muscular dystrophy, sickle cell disease, cystic fibrosis, Huntington's disease; the list goes on and on.

It is clear, however, that as you point out, that there are also ethical issues. Rather than being used to combat disease, it would be possible for genes to be edited in a way that affects, perhaps, intelligence, or athletic ability, or some other so-called desirable traits.

We live in a global world and it seems that the scientific advancements have outpaced the policy in this area.

How do we ensure that this exciting breakthrough in gene editing is used for good by scientists in countries like China or Russia, as well as in our own country?

Dr. KAHN. Thank you, Senator Collins, for that insightful question and comment.

It is the case that scientific advancement outpaces policy in most arenas and, in some respects, that is to be expected. We ought not be making policy before we understand the science as it advances. That is just a feature of areas of biomedical advance.

That said, we do have robust structures for oversight for making sure that the approved technologies are used for the purposes that we intend and not for those that we want to avoid. It is easier to do within our domestic borders, of course, than when we start talking internationally.

I think there is evidence that there, at least, is discussion and an international dialog happening. The National Academies Consensus Committee, that you have heard us mention, is an example of that. That was a partnership, actually. The National Academies of Science in the U.S. was the host, but in partnership with the Royal Academy in the U.K. and the Chinese Academy of Sciences; so to invoke one of the Nations that you mentioned.

The Consensus Committee was actually a year long or a year-plus long process that followed onto an international summit that took place in December 2015. The expectation is that there will be ongoing discussions at a series of additional international summits.

The last I heard about this, there was a proposed summit to be held in China, probably Shanghai, sometime in 2018 as a follow on to the Consensus Report that you have heard us mention. Then maybe in 18 months time, another would be held somewhere in Europe. There is discussion happening internationally as a sort of a long way to say that short point.

Then the last thing I would say is it is the case in our history that prohibitions and bans have led not to control, but rather, quite

the opposite. When technologies are banned in this country, scientists find places where there are either lax or no oversight to go and perform them.

A much smarter approach to policy is strict control to allow careful, responsible science to go forward in ways that are controlled and within our borders, not to push them out.

Senator COLLINS. Thank you.

Ms. Bosley, what questions should parents be asking about the potential opportunities and limitations that are available as a result of this new technology?

Ms. BOSLEY. We actually get outreach from parents on a nearly weekly basis at Editas Medicine because the promise of this technology is so much in the public eye.

I think that a critical factor is the robust nature of the FDA's oversight. Any of these experimental medicines, that come into clinical development in the United States, will go through that process. They have not only the right regulatory authority, but our experience has been very much they are at the leading edge of understanding this science. They are staying current.

It is a fast moving field and they are keeping pace with it, which is, as we would hope and is excellent, they are really understanding of this field and accustomed to rapidly emerging science like this.

I certainly have a great deal of confidence in that oversight mechanism, and I would hope that parents would as well.

Senator COLLINS. Thank you.

Thank you, Mr. Chairman.

The CHAIRMAN. Thank you, Senator Collins.

Senator Murray.

Senator MURRAY. Thank you.

As I mentioned, Washington State has a really strong life sciences sector and is home to several pioneers in immuno-therapy.

Seattle Children's Research Institute has spent the past few years engineering T-cells to fight leukemia and children for whom other treatments had failed. They are collaborating with the biotech firm Casebia on applying CRISPR gene editing technology to alter T-cells to prevent and treat autoimmune disease.

Dr. Porteus, I understand part of your work has involved engineering T-cells to treat and prevent a host of conditions like HIV. Ms. Bosley, I understand Editas has been making progress with the Washington State firm Juno Therapeutics that you mentioned in this area as well.

I wanted to ask both of you, what are the advantages of using CRISPR to engineering the function of T-cells over previous methods? What are the current challenges to advancing T-cell therapies?

Ms. Bosley, maybe if you could start.

Ms. BOSLEY. Yes, thank you for the question.

Immuno-oncology, as you point out, is one of the most exciting, emerging areas of new therapies to treat a wide variety of cancers.

The earliest versions of these therapies—which have been referred to as CAR-T therapies or engineered T-cell therapies—are promising particularly in treating blood cancers and we have seen the first two of these actually achieve FDA approval just recently.

We are really on the verge of an entire new horizon of these therapies.

But there is much more we would like to be able to do, more cancers to treat and improving upon these first steps in immuno-therapy that can be enabled by CRISPR genome editing.

Being able to make additional changes to these T-cells so these T-cells have a wider potential to treat cancer is what is possible with CRISPR. As compared to earlier genome editing technologies, there is a greater flexibility with what you can do with CRISPR.

We do think there is great promise in applying CRISPR to these engineered T-cell therapies to be able to extend the life of the cells that can fight the cancer to be able to treat other kinds of cancers, such as solid tumors not just blood cancers.

Further advancements as we put more edits into the cell, perhaps to be able to have off-the-shelf treatments. Not just ones that are treating the patients with their own cells, but off-the-shelf therapies that can be available to a wider range of patients.

Senator MURRAY. What are the current challenges?

Ms. BOSLEY. There are always challenges of the biology and understanding exactly which genes to edit, but that is also something where the understanding of the T-cell and its role in cancer is moving at a great pace as well.

I think that the active work of Juno and many others in this field is really starting to uncover that biology quite rapidly.

Senator MURRAY. Dr. Porteus.

Dr. PORTEUS. Again, a great question and I will echo Ms. Bosley's comments about the excitement about T-cell therapy to fight cancer.

To get to your question about what does genome editing add that prior ways of genetically engineering T-cells could not give is in two specific areas.

One is the prior ways of engineering a T-cell is that you would introduce a new gene and that new gene would go somewhere in the genome, but you did not know exactly where.

With genome editing, we can actually now take that gene and put it precisely in one location. Now, the entire population of T-cells has the same property, the same potency. It makes for a more homogeneous product, which also means we control the level of that gene much more precisely.

The other thing that you can do with genome editing that you cannot do with a gene addition type approach is you can knockout or inactivate certain genes.

One of the thoughts—and again, I echo what Ms. Bosley said, that we need to understand more of the biology—but one of the thoughts is that when T-cells get activated or tumors grow, they put out molecules that suppress the T-cells from forming or from being active.

What we can do with genome editing is inactivate the inactivators, a double negative, so to speak. Now, release that T-cell to kill the tumor cell whereas prior, it had been inhibited.

Those are the two fundamental things we can do with genome editing that prior technologies did not allow us to do.

Senator MURRAY. Okay. Any challenges to advancing it?

Dr. PORTEUS. Again, I would say we have to understand more of the biology.

I think we have to release the hounds, so to speak, and allow lots of people to explore lots of different variations here so we find what is the best combination? I think if we said, "One company or one investigator is going to find it," we would be limiting ourselves. What we want is a thousand trees to grow because one of them is going to turn out to be the secret.

Senator MURRAY. Okay. Thank you very much.

The CHAIRMAN. Thank you, Senator Murray.

Senator Scott.

STATEMENT OF SENATOR SCOTT

Senator SCOTT. Thank you, Mr. Chairman.

Thank you to the panel for being here this morning.

This is really an exciting topic that I have done some research on for the last year or so, and the more I learn, the more I want to learn to about this topic. It is really one of the miracles that we could see happen for so many patients in the future.

I have had the good pleasure, Dr. Porteus, to work with the Medical University of South Carolina. One of their patients, who is their sickle cell champion, is a little kid named Zion Thomas who has missed a number of days of school because of the pain and the challenges that so many of these youngsters suffer through.

His doctor, Dr. Kanter at the Medical University of South Carolina, has been trying to find new ways and new opportunities to help him go back to school and to live the highest quality of life possible.

I will say that it has been a tragic disease in so many ways, and one of the reasons why is for the last 20 years, there has been really no approved new medicines until this past summer. This is good news.

But to me the CRISPR research and your research, specifically, seem to provide real opportunities, not just to manage the disease, but to eliminate the disease.

I know that you have been approved with a $5.2 million grant to lay the foundation for a clinical trial on potential treatments that use CRISPR technology to, hopefully, eradicate the sickle cell defect in patients' blood. I want to clarify that your research does not alter human embryos.

Can you elaborate on exactly how this treatment would be effective and work, please?

Dr. PORTEUS. Yes, thank you very much.

You have nicely outlined the devastating consequences of this disease and why we need better therapies.

What the strategy that we are developing is the following, which is, that a patient who has the disease and has severe manifestations of the disease initially—because this will be new therapy—will come to our clinic and we will discuss the possibility of going through this, what may be a first-in-human procedure. They will be a very brave person, and we will discuss the potential risks and benefits.

If we believe that the patient understands the risks and benefits, then we will enroll them on the study. I think that is a really key point that sometimes we forget about.

Once they are enrolled on the study, what the process will be is that we will harvest their own blood-forming stem cells. You make the very important point that these are not cells that impact the germline. They are blood-forming stem cells that will stay in the body.

We will then bring them to a specialized manufacturing facility in which we will use the CRISPR technology to change the sickle cell mutation to the nucleotide, the letter that does not cause the disease.

We will measure the frequency that has occurred in that cell population. We will make sure that it passes all of our quality control standards. That it does not have any evidence that we have done something harmful to the population.

Once we have that quality control on the population, we will then bring the patient back and they will undergo what we call an autologous stem cell transplant, in which they will receive high doses of chemotherapy to eliminate all of the remaining blood stem cells that are in the body, and then we will transplant.

Actually, when you do a stem cell transplant that means infusing the cells through an I.V., and the stem cells naturally find their way back to the bones, where we hope our corrected cells will then reconstitute the blood system and the patient will no longer have the disease.

Senator SCOTT. That is amazing.

Dr. PORTEUS. Yes.

Senator SCOTT. In a politically correct word, that is pretty cool. [Laughter.]

Senator SCOTT. Yes, sir. Let me move onto Ms. Bosley here quickly.

I had the good fortune to sit down with one of my good friends, a guy named Dr. Tony Coles, who says that you are a brilliant young lady there.

I added the "young" in, because he would have too.

Ms. BOSLEY. Thank you.

Senator SCOTT. The conversation that we had went in many directions from crops to humans. Part of it is as I look at the opportunity for us to reauthorize bio-defense programs next year, it seems to me that CRISPR could have a positive impact on the inability of mosquitoes to spread Zika, malaria, or other types of diseases.

Can you expound upon the opportunities of the breakthrough technologies in our bio-defense that will be so critically important going forward?

Ms. BOSLEY. Thank you, Senator, for the question.

I agree. Dr. Coles is amazing; an incredible leader in our industry.

Senator SCOTT. Yes, ma'am.

Ms. BOSLEY. In terms of the broad applications of CRISPR, as you note, it is not just healthcare applications and making medicines, which is what we are focused on at Editas, but agricultural and also the concerns that it could be misused.

I think, as Senator Alexander noted in his opening remarks, there are folks who are in those specialized areas looking at this technology and are there protections that need to be put in place?

It is not my area of expertise, but we certainly have sought to also, as a company, make ourselves available to those who are engaged in those questions because we are living and breathing at the edge of this science every single day.

We do feel a responsibility to be a resource for those who are thinking about what kinds of protections might be needed.

Senator SCOTT. Thank you.

I will say, Mr. Chairman, and my parting comment is that someone, somewhere, some Nation will set the ethical boundaries for this conversation going forward. It certainly would be helpful for the United States of America to establish those boundaries to a large extent.

Thank you, Mr. Chairman.

The CHAIRMAN. Well, thank you, Senator Scott.

I know of your interest in this over the last year, so we will treat this as a beginning of a discussion on the subject. We can continue, through roundtables, or hearings, or other discussions, about what responsibility we have to create an environment where all this can succeed.

Senator SCOTT. Thank you, sir.

I look forward to the next hearing, and perhaps we will have one on Cas13, and the next round of RNA, and some things that we can do. That would be kind of cool as well.

Thank you.

The CHAIRMAN. Good. Thanks, Senator Scott.

Senator Hassan.

STATEMENT OF SENATOR HASSAN

Senator HASSAN. Well, thank you, Mr. Chair and Ranking Member Murray.

Good morning to the panel. Thank you for your work and it is great to have a panel that represents the various perspectives and things we need to think about as we engage with this incredible cutting edge technology.

I want to follow-up on what Senator Scott just mentioned and I will ask Dr. Porteus. Much of the discussion around CRISPR is focused on the CRISPR/Cas9 system, which edits sections of DNA with high precision and efficiency.

The technology is promising, but as I understand it, it is not the only CRISPR out there.

Recently, scientists have developed a new type of CRISPR-based system called REPAIR, which stands for RNA Editing for Programmable A to I Replacement, which uses the Cas13 enzyme to edit, not the DNA, but the RNA in cells.

This technology is still a research tool and is not being used in any clinical work. But as I understand it, it could allow for temporary gene editing like turning on and off the alterations it makes.

I understand it is really new technology, but can you explain a little bit more about how this technology might work. What are the

implications of editing RNA versus DNA when it comes to treating and preventing human diseases?

Dr. PORTEUS. Yes, great. Yes, thank you for the question.

First of all, what I would say is that the challenge of taking a discovery in the lab to the clinic requires commitment and focus. One of the things that, I think, Ms. Bosley will say, and I believe in, is that some times you have to pick your horse and run with it as far as you can.

Senator HASSAN. Right.

Dr. PORTEUS. But what is fantastic is behind the scenes now, not even behind the scenes, but behind that horse are people developing more and more tools. The bigger our toolbox is, the more likely we are in the future that we are going to solve all the problems we need to solve.

Senator HASSAN. Yes.

Dr. PORTEUS. What is the potential problem that an RNA editing approach might solve that a DNA editing approach might not solve?

You highlighted it in your question or your statement, which is that RNA editing will be a more transient way of changing how the cell behaves because RNA comes and goes. If the unedited RNA gets replaced, or the edited RNA gets replaced by unedited RNA, your effect will go.

In circumstances where you might only want a transient effect, that would be a really nice way of doing it.

It is possible that we will learn of other things or other problems that we encounter with the standard DNA editing. Having this RNA editing in our back pocket will be good.

I would say that is, if I had to summarize, I think the possibility of doing transient editing for health situations that do not need a permanent change, this is a really exciting way of thinking about it.

Senator HASSAN. Thank you, and I think we will all be excited to learn more about it.

I wanted to ask you another area, Dr. Porteus, because it is my understanding too that CRISPR technology could be useful in the area of anti-microbial resistance.

According to the CDC, at least 2 million people are infected annually with bacteria that are resistant to antibiotics, and at least 23,000 people die each year as a result of such infections.

As I understand it, gene editing can be used to help humans even when the gene editing is not taking place in the human genome.

Dr. PORTEUS. That is right.

Senator HASSAN. For example, CRISPR/Cas9 is being used to specifically target and eliminate harmful bacteria while leaving in place the good bacteria, which makes it difficult for bacteria to develop resistance.

Can you walk us through this a little bit? How could CRISPR help us 1 day combat antibiotic resistance?

Dr. PROTEUS. Yes. So obviously, as an M.D., antibiotic resistance is a huge problem and affects my patients every day, and so, we need to come up with better solutions. There are non-CRISPR based solutions to this problem. I do not want to imply that there

are only CRISPR based solutions to the issue of antibiotic resistance.

But again, we need more tools. So what is a CRISPR based tool that might deal with this problem of antibiotic resistance?

What people are developing is actually the idea that since the CRISPR recognition is so precise, you can design it to cut the DNA of a pathologic bacteria and not the DNA of a non-pathologic bacteria.

The ideal would be that if somebody was colonized in their gut with a mixture of both pathologic and non-pathologic bacteria, they could take a pill which would infect all of the bacteria with the CRISPR, but it would only kill the bacteria that were pathologic and not kill the bacteria that were non-pathologic.

Again, very early day. Has not even really been done too much in animals yet, but it is something that I expect we will see a lot of exciting work over the next five to 10 years.

Senator HASSAN. Well, thank you and my time is up.

To our other two witnesses, Ms. Bosley and Dr. Kahn, thank you for your work.

To all three of you and to the entire scientific community that is working on so much cutting edge developments, just know how much we appreciate what I know is a lifetime of work, and you do not always see the reports right away, and then you get a hearing where we all kind of go, "A-ha!"

You guys are great and we forget to thank you for the years of work and lack of recognition that comes before it.

Thank you.

The CHAIRMAN. Thank you, Senator Hassan.

Dr. Porteus, Ms. Bosley, you have told us, but I want to see if I understand just where we are.

Dr. Porteus, you are working in your laboratory with human beings who have sickle cell anemia.

Is that correct?

Dr. PORTEUS. Yes, so we are working right now with cells.

The CHAIRMAN. Cells from individuals.

Dr. PORTEUS. Human beings with sickle cell anemia.

The CHAIRMAN. Your next step, you were saying, is actually to develop a treatment for an individual.

Dr. PORTEUS. Yes.

The CHAIRMAN. That would be something that is prior to any sort of FDA or NIH approval.

Is that correct?

Dr. PORTEUS. Let me explain.

Before we would ever administer these cells back into a patient, we would have to get FDA approval.

The CHAIRMAN. You would have to?

Dr. PORTEUS. We would have to.

The CHAIRMAN. Have you filed any kinds of papers to do that?

Dr. PORTEUS. What we have had with them is what is called a pre-IND meeting where we have proposed what we want to do. We have proposed that we will do the following experiments, both in terms of efficacy and safety. We have had a conversation going back and forth.

The CHAIRMAN. These are research treatments, basically.

Dr. PORTEUS. They are research.

The CHAIRMAN. That would be approved by the FDA or that the FDA would be aware of?

Dr. PORTEUS. No. What they are is a set of studies that the FDA will say justifies a treatment that could be tried in humans. It would justify giving an IND to allow us to start a clinical trial.

The CHAIRMAN. That is a, quote, "FDA approval" of a treatment.

Dr. PORTEUS. Yes.

The CHAIRMAN. Now, Ms. Bosley, you have not yet filed any application for an FDA-approved treatment to cure, have you?

Ms. BOSLEY. No, not yet.

The CHAIRMAN. But you are about to?

Ms. BOSLEY. Yes. Our goal is to file to be able to begin investigations. Not for approval, but for that first step to be able to test in humans under an investigation.

The CHAIRMAN. Is that the same step he is talking about?

Ms. BOSLEY. It is the same step that Dr. Porteus is talking about, yes. Similar to Dr. Porteus, we have had initial engagement with the FDA.

I think it is an excellent example of their flexibility, particularly for these very new emerging technologies. We work within the Office of Tissue and Advanced Therapies. You are able to engage with them. Of course, there is the very formal documentation, but there is good opportunity for conversation.

The CHAIRMAN. Well, in our 21st Century Cures discussion, we went back and forth in one area called regenerative medicine——

Ms. BOSLEY. Yes.

The CHAIRMAN——and agreed upon some money for some research in the National Institutes of Health, and then an accelerated pathway for regenerative medicine at the FDA.

Do the kinds of investigations and treatments you are talking about fit within that broad umbrella of regenerative medicine?

Ms. BOSLEY. My understanding is the FDA is in the process of implementing the RMAT designation and I think it is a bit of a work in progress.

I am not fully expert in that particular designation, but I think that it was certainly a really promising part of that legislation and possibly could be considered to include this work.

The CHAIRMAN. Well, let me ask it this way.

Do you see, based upon your initial meetings, the need for any changes in the law that would make it more likely——

Do you see obstacles in the law to the prompt consideration of your research and request for investigations? Either of you.

Ms. BOSLEY. Thank you for that question, Senator, because I think one thing that we found is the FDA has the appropriate authority, and they are exercising it well and thoughtfully. I do not see any need for any change in legislation.

I think the continued support of the FDA, the resources, is always critical because in a fast moving field like this, their ability to continue to stay with the edge of the science does depend upon having the correct resources.

The CHAIRMAN. Yes, well, we just approved $9 billion more dollars over the next number of years.

[Laughter.]

Ms. BOSLEY. Thank you for that.

The CHAIRMAN. Dr. Porteus, do you agree with that?

Dr. PORTEUS. I would echo those sentiments exactly.

The CHAIRMAN. Okay. No need for us to write any. Dr. Gottlieb and his team there are paying attention to it.

Dr. PORTEUS. They are.

Ms. BOSLEY. Yes, sir.

The CHAIRMAN. I heard, you may know nothing about this, the mosquitoes that have been referred to several times, I have heard that in other countries that the mosquito which then mates with the altered mosquito is the male or is it the female?

Well, if the male is altered that kills the disease bearing-mosquito. That is being used in other countries but not in the United States because approval of that was hung up at the FDA, and that approval is now at the Environmental Protection Agency.

Do you know anything about that? Is that right?

Dr. KAHN. Yes, I do actually know something.

The CHAIRMAN. What do you know about that? I mean, there are lots of people in South Texas and Florida.

Dr. KAHN. Yes.

The CHAIRMAN. If that is a safe and effective procedure, they would be pretty anxious for it to be available.

Dr. KAHN. Thank you. It is, Senator, a very interesting area and it is not approved anywhere. It has been field tested.

The CHAIRMAN. It has been used in Brazil. Right?

Dr. KAHN. Yes, that is right, and in the Caribbean.

The CHAIRMAN. Did it work?

Dr. KAHN. That is right, in Brazil in a small test area. It has not been approved, I think, for release as a mosquito control approach, but rather, they are trying to see whether it works.

The technology that, I think, you are thinking about is male-altered mosquitoes that are tetracycline dependent. That is, they need tetracycline in their diet. When they are released into the wild, they mate and their offspring are also tetracycline dependent. There is no tetracycline in the natural environment, and so, all of the offspring die.

The CHAIRMAN. Where does this stand now in the United States?

Dr. KAHN. I think, in the United States, there was a proposed field trial in the Florida Keys, but that was seeking stakeholder engagement and input, and then the hurricanes hit, of course. I think that has now been put on hold, so far as I understand.

The CHAIRMAN. Which agency has responsibility? Do you know?

Dr. KAHN. Sorry?

The CHAIRMAN. Which Federal agency has?

Dr. KAHN. I think that was going through the FDA, so it has taken the same path as the Aquasense salmon, if you know that technology.

The CHAIRMAN. Senator Murkowski remembers.

[Laughter.]

The CHAIRMAN. She reminds us about that.

Dr. KAHN. Exactly. She is not here, I think.

The CHAIRMAN. No.

Dr. KAHN. Yes.

The CHAIRMAN. Senator Murray reminds us of that.

Dr. KAHN. The same pathway for approval of that technology would be used for the genetically modified mosquito release.

The CHAIRMAN. Well, I am over my time and Senator Warren is always under hers, so I do not want to set a bad example. But I do have to ask.

Have you noticed any increase in interest in the study of biology as a result of this and other advances in biomedical research?

Dr. PORTEUS. I can say that I have had the opportunity to talk to high school students, and they are so engaged in this technology. Not only about the science, but they love to talk about how it should be applied; the very same issues that all of us in the room are quite interested in. It is really exciting to see.

The CHAIRMAN. Thank you.

Senator Warren.

Senator WARREN. Thank you, Mr. Chairman.

As people have been discussing this morning, the gene editing technologies are already having a transformative effect on healthcare, and I just want to ask more about the underlying research.

Funding from the National Institutes of Health, as well as other Federal agencies, has been critical to supporting the researchers who develop CRISPR and who are putting it to work in all the different areas that we have been hearing about today.

In order for scientists to actually conduct genetic research, they need genetic material. That means the federally funded research that has fueled such exciting breakthroughs in gene editing often involves the collection of bio specimens, things like tissue, and cells, and blood samples from research participants. These bio specimens contain unique genetic information of the people who are participating in federally funded research projects.

That means we have an important responsibility for making sure that our Nation's privacy protections are keeping up with advances in scientific research. Professor Kahn, let me just ask you.

When a researcher generates genomic data through a project that is funded by NIH, is the researcher expected to contribute that data to a Federal data base?

Dr. KAHN. Yes.

Senator WARREN. Yes. Does this genomic data contain information that could be traced back to the individual if it were to become public?

Dr. KAHN. At this point, genomic information is considered identifiable.

Senator WARREN. Okay. I strongly support the data sharing requirements for federally funded research. I think it is a key reason that genetic research has advanced so quickly. But we have to make sure that research participants know that the genetic material that they are turning over is properly safeguarded.

That is why Senator Enzi and I worked together last year to pass the Genetic Research Privacy Protection Act. Our bill requires the NIH to issue certificates of confidentiality to all federally funded researchers. These are the legal protections that ensure that researchers cannot be compelled to release genetic information.

The bill also protects genetic data from FOIA requests, so that the data are only used for research purposes, as intended.

Ms. Bosley, do companies like yours rely on NIH research to develop transformative therapies, support these privacy protections for Federal research projects?

Ms. BOSLEY. Senator Warren, first of all, thank you for the question. Thank you also, for that very kind introduction earlier.

Senator WARREN. You bet.

Ms. BOSLEY. This is a critical issue. There is no question.

As you say, it is critical to patients having the confidence to participate in research, to know that their most personal, identifiable information will, indeed, be safeguarded.

We very much support this, and are very appreciative that you and Senator Enzi have made this such a highlighted issue.

Senator WARREN. Good.

Ms. BOSLEY. Yes.

Senator WARREN. So good for researchers and good for the businesses that are trying to develop this research.

Ms. BOSLEY. Absolutely, yes.

Senator WARREN. Now that this bill has become law, the NIH is moving ahead with the implementation. As of October 1, any NIH funded research that involves the collection or use of bio specimens or genomic data of human subjects will automatically receive this certificate of confidentiality.

Other Federal agencies that fund research—like the CDC, or the V.A., or the Department of Defense—are also rolling out the same protections as we required in this law.

I just wanted to say I am really glad that we were able to get this in our bill when it moved forward, this bipartisan piece of legislation protecting the rights of research participants will only strengthen the work of the scientists and the biotech companies who are doing such exciting work in gene editing.

Thank you very much and thank you all three for the work that you are doing. Just terrific.

Thank you, Mr. Chairman, and I did finish early.

[Laughter.]

The CHAIRMAN. You did. I knew it. Thank you, Senator Warren. Three gold stars to you.

[Laughter.]

Thank you for your contribution and with Senator Enzi. I believe that your legislation was a part of the 21st Century Cures, and is now being implemented, and are very proud of that.

Senator Kaine.

STATEMENT OF SENATOR KAINE

Senator KAINE. Thank you.

I am so happy Senator Warren ceded her time to me, so I can go over.

[Laughter.]

Thank you, all of you, for the testimony, for the work.

I want to talk about two items just for folks who are paying attention to this and talk about what gene editing might mean to treatment of Alzheimer's and dementia. One of the most significant challenges we are facing and it is only likely to get worse. Whether it is the human misery, the burden on caretakers, or the fiscal con-

sequences to families and to the public treasury, this is a mushrooming challenge.

I introduced a bill with Senator Collins and others this week dealing with trying to buildup a workforce that would be capable of providing care to those with Alzheimer's.

But talk about what gene editing might mean for the future treatment of dementia and Alzheimer's?

Ms. BOSLEY. Senator Kaine, perhaps I will comment on that. Thank you for the question because as someone who personally understands the impact of this devastating disease, we certainly all hold hope for being able to help these patients and their families.

It is a tough disease and it is not one where we deeply understand the genetics, and so it is unfortunately not going to be one of the first diseases we are able to approach.

But I think the question is, can we begin to work on it as we deepen the capabilities of the basic technology? Can we begin to work on other neuro-degenerative diseases that begin to point a path toward Alzheimer's?

What I think may also help support those in basic research, one of the aspects of CRISPR as a research tool, so of course, we mostly talk about how you make CRISPR based medicines, which is very exciting.

But in the world of biological research, the ability for CRISPR to unlock scientists' ability to ask and answer new questions, to really understand what underlies Alzheimer's and other terrible diseases more deeply. We are at the beginning of a tremendous revolution there.

I think perhaps the more immediate hope might be, as we better understand what is driving Alzheimer's, can it show us new targets that you might be able to go after with perhaps more traditional pharmaceutical approaches, a small molecule, or an antibody, or something like that?

That may be the area where we see progress that is CRISPR-enabled, but at the basic science level.

Senator KAINE. Thank you.

Additional comments?

Dr. PORTEUS. Maybe I would just like to echo what was said and to give, maybe, a very specific example.

Supposing basic research was funded and you made a discovery that the problem is that cells in patients with Alzheimer's disease were missing a signal to allow them to survive?

Now what you could do with the CRISPR technology is engineer a cell therapeutic to deliver that signal and protect the cells from dying. I do not know what that signal is.

But I know that if somebody told me, "Make a cell that secretes a signal to protect a neuron not to die," I think I have an idea how to do that. I just need somebody to tell me what to make that cell to make.

Senator KAINE. I see.

Dr. Kahn, I have a question for you based on your written testimony. I am just mindful that I have 2 minutes left. You have an interesting bit of testimony on Page 4 of your written testimony.

"Just last week in Canada, a major group of researchers called for a change in their Federal law that makes it a criminal offense

with penalties of up to 10 years in prison for using gene editing tools on cells that could lead to heritable genetic change in humans. The concern expressed by the group is that research has been stopped in ways the Canadian scientists are falling behind their international colleagues."

You then conclude a paragraph later with an interesting bit of testimony.

"There is no comprehensive regulatory approach," and by that, I think you mean comprehensive international regulatory approach.

Dr. KAHN. International. Correct.

Senator KAINE. "However, the absence of which creates an opportunity for some jurisdictions to craft lenient or nonexistent regulation, leading to the emergence of so-called 'regulatory havens,' the encouragement of both scientific flight and medical tourism, and more near-term concerns around scientific leadership and competitiveness, and a loss of the ability to control research that is outside of U.S. jurisdiction."

That is a big concern. We would want to be the leader. We would want to remain in the leadership position in this based upon our institutions and individuals.

How should we start to think about this regulatory issue so that we do not run into a position where we are chasing away—by trying to do the right thing on regulation—we are chasing away innovation to other locations?

The CHAIRMAN. Please take the time to fully answer that question, because that is an important one.

Dr. KAHN. Okay.

Thank you, Senator Kaine, for that. I think you are right. It is a critical piece of this discussion.

As my testimony pointed out, the counterexample to the Canadian example is the United Kingdom, which no one would accuse of having lax oversight. In fact, they have a very strict regulatory control process which allows them to license, in a very narrow way, new and emerging biomedical technologies. It is a permissive regimen with very tight controls. I think that, in fact, is the right approach.

Prohibitions, Canada would be, not effectively a prohibition, but people would behave that way. People do not want to go to jail for 10 years for doing science. Driving people to places either that have more permissive regimes, maybe like the U.K., or to places where there are no rules, which is really what we do not want.

That is bad for a range of reasons as I responded to Senator Collins earlier. Not only does it drive science underground and in ways that we do not get to control it, but we then lack the ability to get that data and the benefits of that research. It disappears, effectively.

We lose in multiple ways when we drive science underground and away from where we want it to be done, which is, I think, in this country and, as you put it, for other reasons like competitiveness and leadership.

This country has long, really forever, been the leader in science in the world and I do not think we want to cede that to anybody else.

Senator KAINE. Thank you, Mr. Chairman.

The CHAIRMAN. Thank you.

Senator Murray, do you have additional questions?

Senator MURRAY. Mr. Chairman, I will submit them for the record.

But I think this has been a fascinating hearing, and I really appreciate all of your intuition, and advice, and knowledge. We have a whole world in front of us that we need to do the right way and your input is extremely helpful.

I know we have more work to do, Mr. Chairman, and I look forward to working with you.

The CHAIRMAN. Thank you, Senator Murray.

Dr. Kahn, do you think we should have any kind of additional regulation on heritable diseases in this country?

Dr. KAHN. Do you mean genetic modifications that are heritable?

The CHAIRMAN. That is what I meant.

Dr. KAHN. Yes. No, just to be clear.

I think that the FDA is in a position in conjunction with the NIH RAC, which we have mentioned, to evaluate technologies that may lead to heritable genetic change.

The NAS Committee that both Dr. Porteus and I have served on listed a set of, I think, ten criteria that would need to be met to consider going forward with anything that might lead to heritable genetic modification.

Some have opined that those ten criteria would be impossible to meet which, in my written testimony, I say if that is the case, then so be it. It is a recipe for a very tight control to allow the benefits to go forward in cases where there is really no other way to achieve a therapy for a particular disease.

An example would be when both parents are at risk or know they would pass on the Huntington's disease mutation. There is no way for that couple to have a child who would not inherit the Huntington's disease gene, which is a horrible, devastating disease and diagnosis.

We might consider that an example where we would have a very tightly controlled way forward for a gene editing approach that would, in effect, create heritable genetic change. But we might see that as a justifiable so long as it was done with the very strict controls.

The CHAIRMAN. Do any of you have a recommendation to Senator Murray, or Senator Kaine, and me, and other Members of this Committee about what we should be doing, if anything, to create an environment in which you can succeed in an appropriate way?

Ms. BOSLEY. Senator, if I may comment on that. It is an excellent question, I think.

In many respects, the 21st Century Cures legislation, there are so many different dimensions of that legislation as well as the long history of bipartisan legislation that comes through this Committee.

I think implementing that robustly really continues to support a fantastic environment for this technology to mature in a careful and thoughtful way.

Dr. PORTEUS. I would say two things. One is a continued sustained—and as a scientist, of course, I would like to say—substantial funding to the NIH for basic science research because as an in-

vestigator taking on real challenges, you have to know that you have the opportunity to spend five, or ten, or even more years on it.

If we see funding go up and down, it discourages people to taking on those long term challenges. I think that is very important.

Then I think—and again, this is consistent with Scott Gottlieb and Peter Marks—is having the FDA have a flexible, data-driven approach to the regulation of this field. It is too new to think that we know exactly which line should be drawn in black ink and which line should be drawn in pencil.

I think we need to have the regulators be data-driven about how we adjust as we get more data from clinical trials about safety and efficacy.

The CHAIRMAN. Thank you very much.

Ironically, the President's—and I do not mean just this President—budget always gets lots of attention and never gets enacted.

It is important for the research community to know that with the leadership of Senator Blunt of Missouri and Senator Murray, who are the chairmen of the Appropriations Committee, and the support of a lot of us, we have increased funding for the National Institutes of Health by $2 billion for two consecutive years and recommended it for a third year, plus the $4.8 billion in the 21st Century Cures.

I mention that not to pat ourselves on the back, but I think it is important to send a signal out through the research community that we are paying attention, and we understand that it is a pretty remarkable time, and we want to attract them.

Senator Kaine asked about Alzheimer's. There is a BRAIN Initiative at NIH and we added money to that. Does any of that make it more likely that this technology could be used to deal with Alzheimer's?

Ms. BOSLEY. Senator, as I mentioned earlier, I think that CRISPR is a fantastic tool to begin to further delve into the biology that can then help us understand how to address the disease itself.

While I cannot state for a fact, I would suspect the researchers benefiting from those funds are absolutely using CRISPR as part of how they are pursuing their science.

The CHAIRMAN. Yes. Okay.

Senator Kaine.

Senator KAINE. Might I ask just one more question?

The CHAIRMAN. Sure.

Senator KAINE. It is probably equally a question for the chair and ranking as for our witnesses.

I know the goal of this Committee is to tackle a Higher Education reauthorization at some point in the near future. In terms of the NIH budget for research, that is one thing, but then so much of the research happens in the universities.

I am wondering whether there are thoughts that we could entertain in connection with the Higher Education reauthorization when we do that. That might also be an accelerator. Assuming that the funding levels, we will work hard to make the funding levels, but are there things that we can do within the Higher Education Act to make the universities as places for this research to be even more

cutting edge? It is already the case, but there might be things we could do in connection with that Act that would accelerate that.

The CHAIRMAN. That is certainly an interesting thought. Senator Murray and I are going to visit this week about higher education and we will certainly consider that.

I do not know the exact figures. I think the numbers are something like $27 or $28 billion of the $36 billion or so in the National Institutes of Health are spent at research universities in this country. That is where most of it goes.

I want to ask you as we conclude, would you be willing to say what you think the three or four? You mentioned, there are 6,000 diseases and 95 percent of them do not have a treatment. We have talked about sickle cell anemia.

What are the three or four other diseases that are most promising for cures from the CRISPR technology?

Ms. BOSLEY. Thank you for that question because the hope and promise of this technology is what excites all of us.

I am always a bit cautious over the word "cure," because we certainly have to provide durable benefits to patients, but it is a big word. I want to make sure we are not over-promising too soon.

Other diseases where people are applying CRISPR, there are other eye diseases such USH2A, which is a genetic disease of the eye. There are other blood diseases such as Beta Thalassemia. There are diseases of the liver that are genetic diseases of the liver.

It really does span across a range of other diseases that because this technology is so broadly applicable, people are pushing it in many different directions right now.

Dr. PORTEUS. Yes, as I said before, the great thing about this technology is it is a platform technology.

If we figure out, and we as a community figure out, how to cure sickle cell disease with just some subtle tweaks, subtle changes in the reagents. We now can cure Severe Combined Immunodeficiency, Bubble Boy disease; other primary immuno-deficiencies; other genetic diseases of neutrophils in the immune system; other genetic diseases of the blood. It does not take a whole new development to move from one disease to the next.

What I really think is important is that we develop two or three cures, I am going to use the word "cures," because I will be an academic about it for diseases of the blood, and then we need to develop two or three cures for eye diseases. Because once you have cures for one disease in an organ, that is the platform for the hundreds of other diseases in that same organ.

The CHAIRMAN. Dr. Kahn.

Dr. PORTEUS. The liver, eye, brain, blood.

The CHAIRMAN. Would you add to that at all?

Dr. KAHN. Well, I think Matt's point in particular, is really important because one thing that we want to make sure is that the benefits of these therapies are shared widely and with diverse populations.

I think the idea is that these are platforms which can then be wrapped up and used in many other diseases, and not just focus on the diseases that affect the most people.

The CHAIRMAN. Yes.

There is, at the beginning of Thomas Friedman's book, when he talks about 10 years ago in 2007, Steve Jobs and John Doerr were at a soccer game and Jobs showed him the iPhone. Their discussion was about who should do the apps. Apple was planning on doing the apps and I think maybe Doerr said, "Why do you not let everybody do them?" That was a pretty big decision.

That is the kind of platform you are talking about. Figure it out, and then let the world copy it, and see how many different inventions we can come with.

Well, this has been a fascinating discussion. I thank Senator Murray for her participation in this.

I would confess that I told the witnesses, Patty, that I was fishing in Canada in August, and I only listened to the Canadian Broadcasting System to get the weather, and on came an interview about CRISPR. I stopped, and I listened, and I was fascinated with it, and I took notes. I said, "One of the privileges of being Chairman of this Committee is I can have a hearing on that."

[Laughter.]

That is this hearing.

I imagine those who listened today are having the same thinking about this, as well as students who are in high school or college wondering what their major ought to be. This is a fascinating future.

I would like to ask unanimous consent of the statement, by Dr. Marcy Darnovsky of the Center for Genetics and Society, be submitted into the hearing record.

The record will remain open for 10 days. Members may submit additional information for the record within that time, if they would like.

This Committee will meet again tomorrow, November 15 at 10 a.m., for a hearing entitled, "Encouraging Healthy Communities: Perspective from the Surgeon General."

Thank you for being here.

The Committee will stand adjourned.

[Additional Material Follows]

RESPONSE BY MATTHEW PORTEUS TO QUESTIONS OF SENATOR COLLINS, SENATOR MURRAY, SENATOR BENNET, AND SENATOR WHITEHOUSE,

SENATOR COLLINS

1. Advancing and linking animal models to cures is critically important in this endeavor. In a blog post earlier this year, NIH Director Dr. Francis Collins wrote about the promise of CRISPR gene editing in mouse studies in the area of Huntington's Disease as well as ongoing questions and potential safety concerns. In Maine, the Jackson Laboratory (JAX), distributes more than 3 million mice annually to more than 25,000 investigators in 60 countries each year. JAX received an NIH grant that will utilize CRISPR to generate, breed, cryopreserve and clinically assess the health and well-being of 1,000 lines of mice. The research team will work with the scientific community to select genes of interest that are predicted to function in select pathways of clinical significance. JAX has also received additional grant dollars to support research to improve the accuracy and efficiency of genome editing for research, drug testing, and future therapeutic delivery.

Question. Dr. Porteus, as NIH looks to advance this technology, what types of resources or funding opportunities are most needed?

Answer. Thank you for this very important question that goes to the heart of how to keep the United States at the forefront of cutting edge and transformative research like genome editing and CRISPR/Cas9.

The support of JAX by the NIH to generate, breed, cryopreserve, and clinically assess 1,000 different lines generated by genome editing and the CRISPR technology is just one of the many different productive ways that the NIHcan advance this technology. In addition to supporting JAX, one of the key resources in the biomedical research community, it will be important for the NIH provide resources in at least these three areas:

1. ***Continued broad support for scientifically sound, peer reviewed, basic science research***. The CRISPR technology arose out of scientific research that was unrelated to its use as a powerful genome editing tool. Nobody predicted that by studying how bacteria protect themselves from infection would lead to the discovery of arguably one of the most powerful tools in biomedical research. This is just one example out of many of how of basic research leading to unexpected discoveries that have tremendous positive impact on human health.

2. ***Increased support for the next generation of scientists with the development of career opportunities in biomedical scientific research***. It is this next generation of scientists who are going to use technologies like CRISPR and genome editing to improve the lives of people in the United States and around the world in ways that we cannot even imagine now. The vitality of the biomedical research enterprise in the United States depends on the strong financial support of talented and creative trainees throughout the country. This includes supporting programs to engage high school scientists in the thrill of biomedical research, support of undergraduate students interested in STEM careers, support of graduate students as they begin to develop their expertise, support of post-doctoral trainees as they transition to independent careers, and early independent investigators. The training time for a person interested in becoming a scientist who might make discoveries like CRISPR in the future is much longer than in other fields and sustained support from the NIH and the Federal Government for these people is essential. Finally, increasingly innovative and cutting edge biomedical research is done as teams—the NIH should find mechanisms to increase the support and rewards for scientists who participate as valuable Team Members rather than primarily rewarding the top of the scientific food chain.

3. ***Increased NIH support for translational efforts for rare diseases***. While each disease may only affect tens of people in the United States, in sum these rare diseases affect the lives of tens of millions of people in our country at great social, personal and economic harm. Traditionally the NIH has not provided the larger dollar amounts that are necessary to translate a discovery in the lab to an approved therapy for patients for rare diseases. Since private entities are reluctant to make these investments because the diseases are not likely to generate high revenues because of their rarity, it would accelerate therapeutic CRISPR/Cas9 genome editing for the NIH and other Federal agencies to step into that breach and provide the support needed to develop cures for rare diseases.

SENATOR MURRAY

1. In the 21st Century Cures Act, I pushed to secure nearly $5 billion in Federal funding for the National Institutes of Health (NIH) to bolster specific initiatives and to allow the agency to dedicate more of its discretionary funding to basic research. Federal support for this type of research is especially important for advancing cutting edge technology as private entities are less likely to invest in basic research when it is unclear what the end product will be. As investments like these work to further research using CRISPR and other gene editing technology, we must also prioritize upholding the highest ethical standards as we support continued advancements.

Thank you for securing the additional funding for the NIH as part of the 21st Century Cures Act! It is funding like this that will keep the United States at the forefront in developing cures for patients who currently do not have cures.

Question A. Can you comment on the benefits of having support and funding from NIH and other Federal agencies for research using CRISPR and other gene editing technologies?

Answer. The United States has been a world leader in biomedical research and the development of transformative technologies like CRISPR and gene editing technologies because of the sustained support of the NIH for scientifically sound, peer reviewed, basic, translational and clinical research. It is well acknowledged that it can take 20, 30, or more years to go from a creative idea to a commercial therapy that impacts the lives of patients. Almost always support from the NIH has been a critical part of this process, particularly in the early stages. Where the NIH can begin to help accelerate the process is for the agency to have additional resources

to support the middle translational stages. There are hundreds if not thousands of diseases that the genome editing and CRISPR technology might address, many of them rare but devastating diseases which might not attract the investment of biotechnology or pharmaceutical companies, and with increased support these can all be developed. The relatively recent formation of the National Center for Advancing Translational Sciences (NCATS) is a good step in this direction but NCATS remains relatively under funded to fully support the broad vision and mission it has. The funding for translational research for rare diseases across the other NIH institutes is also less than optimal and if it was increased could accelerate the development of the next generation of cures for patients who currently have no good treatment.

On a personal level, the support of the NIH has been instrumental in our development of genome editing and CRISPR/Cas9 to treat genetic diseases such as sickle cell disease, severe combined immunodeficiency ("bubble boy disease") and HIV. The support from the NHLBI and NIAID through KO8, R21, and R01 funding mechanisms have allowed me to hire the best people and perform the cutting-edge experiments that has brought us to the brink of being able to apply the technology to cure people of these diseases in the next 2–5 years.

Question B. Are there specific circumstances in which current restrictions are limiting scientists' ability to conduct research in the United States and compete with efforts in other countries?

Answer. The United States continues to be a leader in genome editing and CRISPR/Cas9 technology though there are scientists from other countries who have also made and will continue to make important contributions. In my direct field of using genome editing of somatic cells to treat disease, there are no current restrictions that are impeding our ability to compete with scientists in other countries. Because of the current restrictions on human embryo research in the United States, it is likely that scientists in other countries will lead in using genome editing technology to better understand the fascinating process of early human development. I recognize that this policy choice, however, is based not just on scientific and biomedical research considerations.

Question C. Are there countries that have managed to establish guidelines that maintain ethical standards but better allow for advances in applying this technology?

Answer. Thank you for this very probing question. I think that many countries are currently thinking carefully about the right standards by which genome editing research should be carried out within its borders. For somatic cell editing to treatdisease, I believe that, in general, the United States has as clear ethical and regulatory standards as any country in the world. As the technology develops, I hope that the FDA will be able to be flexible and adapt to new information to continue to put United States at the leading edge.

The United Kingdom has established the Human Fertilization and Embryology Authority (HFEA) which provides a mechanism to assess the ethics and scientific quality of research involving human embryos. This structure will probably permit the U.K. to lead in the ethical use of genome editing to understand early human development.In contrast to the United States where currently such research is prohibited using Federal funds and there is no mechanism to evaluate the ethical and scientific considerations for such experiments. This lack of a formal mechanism of evaluation by experts means that research using private funds might occur without ethical and scientific assessment. In contrast, in other countries, like China, it is essentially unregulated and thus at higher risk for un-ethical experiments to be performed. Thus, the question is on point in identifying the continued need to develop a Goldilocks ("just right") approach to establishing guidelines.

At the hearing, several Members of the Committee discussed the need not only for the United States not only to be a scientific leader but also an ethical and regulatory leader. I share that sentiment and believe there is an opportunity for the United States to be that leader.

SENATOR BENNET

1. Five years ago, we passed Breakthrough Therapies on which I worked with Senators Burr and Hatch. Our goal was to create more regulatory certainty at the FDA so that innovative breakthroughs can reach the patient as soon as possible. The FDA has now approved over 60 breakthroughs.

In Ms. Bosley's testimony, she indicated "success in this field will depend in part upon Congress maintaining the robust, but flexible, regulatory system."

Mr. Porteus wrote that "for first in human uses of genome editing, the current regulatory structure is appropriate. But if genome editing strategies are shown to

be safe and are based on a shared platform, the regulatory agencies should have the flexibility to standardize a core set of experiments to allow investigators to bring transformative therapies in a more streamlined fashion to patients."

Question A. Is our regulatory framework equipped to keep up with gene editing?

Answer. Thank you for working with Senator's Burr and Hatch on establishing the Breakthrough Therapies pathway. I think the field of cell and gene therapy is very pleased with how this pathway has accelerated the development of new treatments. A recent study shows successfully resulted over the last five years in a significantly lower median drug development time (4.8 years) than drugs without an accelerated pathway (8 years; Hwang TJ, et al., 2017, JAMA 318(21):2137–2138). Complementing this important regulatory path has also been the Orphan Drug Tax Credit which has also been very important in providing positive incentives to the private/business sector into developing therapies for patients with rare diseases. According to an analysis by the National Organization for Rare Disorders and the Biotechnology Innovation Organization, approximately 33 percent fewer orphan therapies would have been developed over the last 32 years without the Orphan Drug Tax Credit. The development of additional incentives to compensate for the possible decrease in this tax credit could be beneficial in stimulating the development of therapies for rare diseases, including rare childhood cancers.

Thank you for following up on my and Ms. Bosley's testimony regarding what I believe is an important pragmatic issue in the field. The leadership of the FDA has made it clear that the agency wants to provide regulation based on scientific evidence. In my interactions, I have been generally impressed with the agencies willingness to engage in the science of genome editing. They clearly recognize that they need to keep up with the rapidly moving science of genome editing and CRISPR/Cas9 technology. That being said, the FDA is not known for being the nimblest of organizations, so it remains to be seen if they are able to keep up with this rapidly moving field. Activities that empower the FDA to be able to act more flexibly and nimbly should help accelerate the ability of transformative genome editing based therapeutics to reach early clinical trials and then become commercially approved. In addition, keeping up with this rapidly developing field will require the FDA to be fully staffed and well informed which will require sufficient funding to do so. The American Society of Cell and Gene Therapy (ASGCT) is interested in helping the FDA in keeping abreast of the latest developments and as a Board member of the ASGCT I would help facilitate the ASGCT organizing such an effort. The FDA approval of three gene therapy products in 2017, however, highlights that the FDA is currently doing a good job in not inhibiting novel cell and gene therapy therapeutics from reaching patients as rapidly as possible within an appropriately prudent structure.

Question B. (For Mr. Porteus) Can you expand on how standardizing a core set of experiments can bring these therapies to patients in a more streamlined fashion?

Answer. Establishing transparent and scientifically based standards would accelerate the translation of genome editing based therapies. Currently, each group developing a genome editing or CRISPR based therapy has to negotiate with the FDA about what efficacy, safety and toxicology studies are needed to initiate clinical trials and then to gain approval. This results in every group more or less having to re-invent the wheel. In many ways, however, genome editing and CRISPR/Cas9 are platform technologies whereby a program focused on one disease will be nearly identical except for perhaps only subtle differences, from a program focused on another disease. Because of this similarity, the two programs are likely to have very similar safety profiles. Yet, under current guidelines the FDA evaluates the two independently. By establishing a core set of safety standards for a given platform, it would give clarity to independent groups on what they needed to do and funding sources a clearer sense of what levels of support would be needed. Moreover, by establishing standards it should also increase the efficiency by which the FDA could evaluate new programs. In this way, a group developing a genome editing therapy in Colorado would no have to go through potentially different process than a group developing one in Washington, California, Massachusetts or any other state. These standards should be based on scientific evidence rather than theoretical concerns or hypothetical scenarios. I believe the National Institute of Standards and Technology (NIST) has initiated a project to help develop genome editing safety standards that the FDA might adopt.

2. This year, I worked on the RACE for Children Act with Senator Rubio, which directs pharmaceutical companies to study some of the most innovative cancer drugs for children when the treatments are effective for adults and there may be a benefit for kids.

During this process, we heard about some of the challenges in conducting clinical trials for childhood cancers because they affect fewer kids.

As a practicing pediatric oncologist, I thank you and Senator Rubio for working on the RACE for Children Act. While we as a field have made tremendous progress in treating children with cancer, there remains much work to be done and incentivizing pharmaceutical companies to study innovative cancer drugs in children will have great impact.

Question A. Do you expect similar challenges when it comes to genome editing to treat childhood diseases including different cancers?

Answer. There are similar challenges to applying genome editing to treat childhood diseases. The similar challenge is that many of the diseases that might be cured by genome editing are rare or so called "orphan" diseases. Developing a new therapeutic, especially one using a cutting-edge modality like genome editing, requires a substantial investment and commitment in time, resources, and money. As just one example, a regulatory path that might be appropriate for a common disease, might simply be too burdensome for a rare or orphan disease. Thus, finding mechanisms to give incentives to develop genome editing therapies and developing an efficient and streamlined regulatory path for rare/orphan diseases are both essential.

Question B. What else should we be doing to ensure that kids with rare cancers have the same access to innovative gene therapies?

Answer. In addition to legislation like the RACE for Children Act and the ability to extend patent lifetime by testing a therapy in children, an important part of ensuring that children with rare cancers get access to innovative gene therapies is to ensure that there is strong funding for investigators to test and develop therapies for children. The improved treatment of childhood cancer has been catalyzed by funding organizations who are dedicated to finding better therapies for pediatric cancer. The budgets of these committed organizations, however, pale in comparison to the annual budget of the National Cancer Institute (NCI). While Congress should not get into the weeds about which research grants to fund or not, high level guidance about making the funding of programs directed at rare childhood cancers a high priority would be important.

In addition, bringing an innovative new therapy to market is costly. Companies will make economic decisions that developing therapies for rare childhood cancers is not cost effective even if the science and biology suggests it is extremely promising. Thus, creative ways to make sure that economic arguments do not impede the development of such therapies would be extremely helpful. Such mechanisms might include creating better ways for public-private partnerships to work for both sides or for there to be ways for entities like the NIH to de-risk the development such that it would be more cost effective for a company to develop an innovative gene therapy for a rare childhood cancer.

While there are appropriately higher standards for testing novel therapies in children, there is a risk that the higher standard will disincentivise such development. For many diseases, the earlier in childhood that it is treated, the more successful the outcome. Thus, the FDA should not put undue restrictions in bringing innovative therapies to younger patients where they are likely to have the most impact.

The FDA Regenerative Medicine Framework includes a guidance that encourages adaptive study design (evaluating the study parameters at one or more times during a trial and adjusting them as needed), as well as use of novel study endpoints, which could both contribute to earlier access to approved therapies. FDA grants for natural history studies of rare diseases has also been a positive step this year, as was the partnering on this effort by the NCATS Therapeutics for Rare and Neglected Diseases program. Such research can inform clinical trial development, and may lead to the use of natural history models to augment or replace placebo arms in studies of therapies for very rare diseases, for which trial recruitment can be difficult and for which withholding treatment may pose ethical concerns. Therefore, maximizing funding to the FDA Orphan Products Grants Program and the NCATS Therapeutics for Rare and Neglected Diseases program could be beneficial.

3. In Colorado, there are researchers at our universities using gene editing, specifically CRISPR to cure difficult conditions. At CSU, they are using the technology to delete the HIV genome from infected cells in order to cure the cells and ultimately get rid of the disease.

Question A. How is academia currently aligned with industry to maximize the progress we are seeing in gene editing?

Answer. The use of genome editing and CRISPR to provide novel therapies for HIV is an extremely exciting application of the technology.

The development of an innovative new therapy, such as by using CRISPR to delete the HIV genome from infected cells, requires both academia and industry. The nimbleness and scientific risk taking that is encouraged in academia is essential to get such projects off the ground. Industry is essential to bring such therapies to market. There remains, however, what is colloquially called "the valley of death" in which many exciting ideas that have been developed in academia end up dying as they attempt to be translated. There are multiple reasons for this, including that some ideas developed in academia turn out on further scientific examination not to be good therapies, but improved alignment between academia and industry would minimize the attrition. At Stanford and other institutions experiments are underway in which industry develops closer alignment with academia in the early stages of research including through unrestricted funding, through direct partnerships, through having academic trainees spend dedicated time working in industry as part of their training, and others. These experiments need to be carefully monitored, however, so as to assure that academic researchers do not develop conflicts of interest that bias their research and restrict their freedom and nimbleness. If successful, however, these partnerships should enhance how both sides think about more efficiently translating exciting ideas in academia to true therapies for patients.

Question B. What else can we do to stimulate genome editing research in academia?

Answer. The most important way to stimulate genome editing research in academia is to assure that sustained and substantial funding is available for researchers to take chances on innovative ideas. Since genome editing was developed out of seemingly unrelated basic science work, this means continued support for basic science research—we can never predict from where the next exciting breakthrough technology like CRISPR might come from. In fact, we can usually be sure it will come from some place nobody predicted ahead of time. Since innovative discoveries and ideas are most likely to come from young and nimble minds, it means dedicated funding should be directed toward training the next generation of scientists and funneled primarily to senior investigators, even those who have a long track record of success, who have established their set ways of thinking of problems. (A my own career transitions to "Senior Investigator hood," I will perhaps regret this statement in the future. . .). Finally, increased dedicated investments in translational research and translational research training to allow people to cross "the valley of death" will stimulate academia to develop genome editing.

Question C. Are there steps we need to take to harmonize efforts internationally?

Answer. The recent National Academy report entitled "Human Genome Editing: Science, Ethics, and Governance" (*http://nationalacademies.org/gene-editing/consensus-study/*) emphasizes the importance of harmonizing the efforts of regulating genome editing internationally. The National Academies, in conjunction with the Royal Academy of Britain and the Chinese National Academy Sciences are planning to have regular conferences to facilitate ongoing discussions regarding harmonization. In addition, there are multiple other efforts to do the same. These discussions need time to mature, however, before any formal guidelines might be established. The field is developing too fast for people to know how to gently and appropriately develop such harmonization.

Question D. How can we further support the progress that academia is making in genome editing?

Answer. In addition to assuring sustained and substantial funding as discussed in question B., showing continued interest in understanding the technology without politicizing the technology would be great support. While scientists are inherently self-motivated, there is no doubt that as human beings we take on our tasks with renewed efforts and energy when we see that what we are working on is seen as important and impactful by others. The American Society for Cell and Gene Therapy, the leading scientific organization in the field, is excited and willing to help educating the public and Congress about the science and ethics of genome editing and CRISPR/Cas9 technology.

SENATOR WHITEHOUSE

1. The National Academy of Sciences/National Academy of Medicine report on gene editing discussed the challenges that remain in minimizing unintended results, or "off-target effects," when gene therapy is administered to patients. The National Academies report concluded that there is "no single acceptable off-target rate," and that the acceptable amount of unintended effects will depend on the situation.

Question 1. In your work, how do you assess the off-target effects of a therapy, and what criteria do you use to weigh the benefits of a therapy versus the costs of its off-target effects?

Answer. This is a very important question for which in this rapidly developing field there is currently no clear answer. As we learn more, particularly from the first human clinical trials using genome editing and CRISPR/Cas9 technology, we will be more informed to come up with better answers. In the meantime, it is why we need to be flexible in thinking about how to regulate genome editing technology so that we can adapt to new information.

In our own research, we take the issue of potential off-target effects seriously and use the best valuable technology to both measure and reduce such potential effects. Using such methods, we now find that the frequency of off-target effects for the systems we use is likely below the background frequency that changes occur in the genome of cells naturally. In addition, we pay close attention to whether cells that have been modified by genome editing show any aberrant or abnormal behavior. So far, we have never seen that happen. These results give us comfort but we still remain vigilant. The field continues to develop better methods to both measure and reduce potential off-target effects.

That being said, we also recognize that the diseases we are developing genome editing to treat, such as sickle cell disease, are life-threatening diseases with continued need for better therapies, including cures. Thus, while we remain vigilant about potential off-target effects we are also pushing the technology to early clinical trials in a prudent but rapid fashion. Ultimately, the true efficacy and safety of genome editing technologies will only be determined such clinical trials and cannot be fully assessed by studying cells in a petri dish or a mouse model.

The FDA shares this view that a scientific analysis of potential risk/benefit is the best way to safely bringing this new approach to curing patients to patients in a timely fashion.

2. Gene editing technologies like CRISPR hold incredible potential for treating or even curing diseases for which there are currently no available therapies.

Question A. Given this potential, is gene editing research currently receiving adequate Federal support?

Answer. Increased Federal support would accelerate genome editing research. More funding to the NIH would support biomedical research in general, since currently the NIH is only able to fund approximately 19 percent of grant applications. While many scientifically strong genome editing programs do receive Federal grant support (my lab, for example, has been fortunate enough to be funded by the NIH for our genome editing research), there are many other scientifically strong programs that do not. These unfunded projects are missed opportunities for the field. NIH Director Francis Collins indicated during the HELP Committee hearing on the implementation of the 21st Century Cures ACT that early in the 21st Century, when more funding was available, 30–35 percent of grant applications were funded. Dr. Collins stated that the NIH at that time found proposals that scored up to approximately the 30th percentile of the total were of a similarly high quality. Therefore, more funding to the NIH could fund a great deal more quality research. In addition, funding targeted innovative research as defined in the National Biomedical Research Act, could also be beneficial to genome editing research.

It is important to emphasize that the key to supporting this research is sustained funding. The development of a good genome editing idea takes years. While short 1–2 year funding can allow scientists to do preliminary testing, it takes much longer to fully scientifically develop and prove the idea.

Question B. Would additional Federal investment help spur advancements in gene editing technologies, and if so, what specific areas of research would you like to see additional investment in?

Answer. The specific areas that I would like to see increased Federal investments in are the following:

1. Increased funding for training of the next generation of scientists. These are the scientists who will build on what is being done now and develop even broader applications of the technology.
2. Continued funding for basic science research—the engine that drives that biomedical innovation. The best tools in genome editing research, for example, were developed out of fields that were seemingly unrelated and were investigating the basic science of different biologic processes.
3. Increased funding for translational research to facilitate ideas being able to successfully traverse "the valley of death." Translational research is more costly than basic science research for various reasons, including that it requires larg-

er, more plex teams of investigators and has different timeframes. In addition, translational research, almost by definition should not be innovative even though it is impactful. The NIH has historically not had good mechanisms to fund translational research teams and projects.

4. Increased funding for core infrastructure to help accelerate research. Exciting discoveries are often made in places where it is not readily possible to take the next steps. The Federal Government could accelerate genome editing by establishing centralized core expertise to help such researchers move to the next steps. Such core infrastructure would be a relatively new endeavor for the NIH. This core infrastructure could developed as a partnership with industry. The details of such a partnership, however, would be critical in order not to compromise the integrity of the NIH and the academic investigators by creating real and apparent conflicts of interest.

3. In the 2016 Worldwide Threat Assessment of the U.S. Intelligence Community, former Director of National Intelligence James Clapper included gene editing as a potential weapon of mass destruction and proliferation, stating, "Given the broad distribution, low cost, and accelerated pace of development... its deliberate or unintentional misuse might lead to far-reaching economic and national security implications."

Question A. How far is gene editing technology from posing a serious national security threat?

Answer. The potential for misuse of genome editing is clearly possible and careful thought about how to prevent such misuse is important. On the other hand, many of these worries are theoretical at this point and it is important that such worries do not create a climate of fear around the use of genome editing technology. For example, there is speculation about whether genome editing could create "super-soldiers." While this idea is fun to speculate about, my assessment is that the scientific feasibility of genome editing being able to create "super-soldiers" is essentially nil. If this theoretic fear about creating "super-soldiers" contaminates the thought process about using somatic cell genome editing to cure disease, we will have done a disservice to the millions of patients who might benefit from genome editing based therapies.

The potential destructive use and security threat by either the overt or inadvertent use of genome editing to alter our ecology, environment, or food supply is outside my area of expertise but seems like a potential security threat that needs to be evaluated and monitored on a continual basis. Again, we need to be careful that such evaluation does not create a climate of fear that might impede the use of genome editing to create a safer, more robust, more humane and more efficient food supply.

Question B. What steps can the United States take now to reduce the potential threat of the misuse of gene editing technology?

Answer. The most important step that the United States can take to reduce the potential threat of the misuse of genome editing technology is for it be a leader in assessing this risk in a balanced, transparent and scientifically justified manner. By being such a leader, the United States can help establish the scientific and ethically permissible uses of genome editing and then also establish consequences that the international community would commit to for those who violate those standards.

Response by Katrine Bosley to Questions of Senator Murray, Senator Casey, and Senator Whitehouse

senator murray

1. While the Food and Drug Administration (FDA) has not yet approved any CRISPR therapies or products that use CRISPR in the manufacturing process, it is important the agency has the right authorities and expertise in place to ensure these products are effective, and safe long-term. One of my top priorities during 21st Century Cures was ensuring FDA had new hiring authorities to make it easier for the agency to recruit and retain the best scientific talent.

Question. Are there additional authorities or resources that FDA needs from Congress to effectively regulate these products?

Answer. In short, no new authorities or regulations are needed. FDA already possesses a robust but flexible regulatory framework that has worked well overseeing biotechnology products for over forty years, including nearly thirty years of gene therapy experience and several recent years with genome editing technologies. Editas Medicine also appreciates the Committee's leadership in recently enacting

the 21st Century Cures Act. We view the Act's Regenerative Medicine Advanced Therapy (RMAT) designation as a positive regulatory development that, when applied to genome editing products, would allow novel, innovative medicines to access FDA's existing expedited review programs.

Thus far, FDA has also taken initiative staying informed of advances in genome editing and has thoughtfully reached out and collaborated with both industry and leading academic centers alike. These efforts have helped to ensure the continues to understand the State of the science in this fast-moving field. The leadership at CBER and the Center's new Office of Tissues and Advanced Therapies have done a commendable job in this regard.

We believe it would be particularly important for the Committee to support and encourage FDA's continued stakeholder engagement and scientific exchange with leading researchers in the genome editing field. It will be critical, as the science and technology of our field advances, for FDA to sustain this dialog through regular and structured fora with universities, leading scientific societies like the American Society of Gene & Cell Therapy (ASGCT), and industry groups like BIO.

SENATOR CASEY

1. According to James Clapper, former Director of National Intelligence, gene editing may pose a risk to national security. In his statement for the record at a hearing before the Senate Armed Services Committee last year, Clapper testified that "given the broad distribution, low cost, and accelerated pace of development of this dual-use technology, its deliberate or unintentional misuse might lead to far-reaching economic and national security implications."[1]

Question A. Based on your familiarity with the technology, please comment generally on the potential national security risks associated with it.

Answer. While it can be conceived in the broadest sense, applications for bioterrorism are beyond the scope of our expertise at Editas Medicine. What we can speak to is the tremendous potential of genome editing technology to advance human health in the years ahead. Should the Committee wish to explore potential national security issues further, it would be our pleasure to reach out to our scientific founders and other third-party groups (such as BIO) to facilitate additional learnings in this area.

Question B. In your opinion, is there a need for additional biosafety and biosecurity regulations to protect laboratory workers who use gene editing in their research? What precautions do staff in your labs take to ensure biosecurity?

Answer. No additional regulations are needed, in our view. With respect to biosafety and biosecurity, genome editing is no different than other recombinant DNA technologies for which policies and best practices currently set by the NIH and CDC have been evolving since the 1970's. Examples include standardized classifications of laboratory biohazard levels and corresponding standards of practice, protective equipment, qualifications and procedures.

2. One of the recommendations borne out of the recent National Academy of Sciences/National Academy of Medicine International Study Committee entitled "Human Genome Editing: Science, Ethics and Governance" was that researchers should incorporate public engagement to assess the risks and benefits of genome editing technologies.[2]

Question A. As Editas is working on a product to correct vision loss and blindness, how is the blind community being consulted and included in your work, the development of products, and in overseeing and evaluating the research?

Answer. We strongly agree with the Academies' view of the importance of public engagement and dialog. We believe that it is essential to develop ocular therapies through a collaborative process with patient organizations that represent the blind community. We have an established relationship with the Foundation Fighting Blindness (FFB) as well as many local and international patient advocacy groups with whom we consult regularly. These organizations are supporting our efforts to enroll our recently announced LCA10 Natural History Study, a non-interventional

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[1] James Clapper. *Worldwide Threat Assessment of the US Intelligence Community*. Senate Armed Services Committee Statement for the Record. February 9, 2016. *https://www.armed-services.senate.gov/imo/media/doc/Clapper_02-09-16.pdf*

[2] National Academies of Sciences, Engineering, and Medicine. 2017. *Human Genome Editing: Science, Ethics, and Governance*. Washington, DC: The National Academies Press. *https://doi.org/10.17226/24623*

study designed to advance our understanding of disease variability and inform our clinical development plan.

Question B. How are you addressing any potential concerns raised by advocacy communities and stakeholders, including those with disabilities, as you design clinical trials?

Answer. We are actively engaged in an ongoing dialog with the blind community through the patient advocacy organizations that represent them. We believe that we are well-positioned to learn of any questions or concerns that may exist within the community and are committed to open and transparent communication.

3. As the first gene therapies are coming to market, we are seeing manufacturers and payers consider new types of outcomes-based payment arrangements to mitigate the high costs of these drugs. However, I remain concerned that new gene therapies may end up being unaffordable for the patients who need them.

Question. How can we ensure these technologies, once in use, are affordable for all Americans?

Answer. The U.S. reimbursement system was built to pay for comparatively smaller increments required every year to manage people's chronic diseases. We believe that an evolution must take place within the reimbursement system to support access for all of the Americans that need these potentially transformative therapies. This evolution includes the implementation of value-based models of reimbursement. As part of this, we are actively participating in multi-stakeholder consortiums with leaders from across healthcare and academia aimed at informing the changes required to support this evolution.

SENATOR BENNET

1. Five years ago, we passed Breakthrough Therapies on which I worked with Senators Burr and Hatch. Our goal was to create more regulatory certainty at the FDA so that innovative breakthroughs can reach the patient as soon as possible. The FDA has now approved over 60 breakthroughs.

In Ms. Bosley's testimony, she indicated "success in this field will depend in part upon Congress maintaining the robust, but flexible, regulatory system."

Mr. Porteus wrote that "for first in human uses of genome editing, the current regulatory structure is appropriate. But if genome editing strategies are shown to be safe and are based on a shared platform, the regulatory agencies should have the flexibility to standardize a core set of experiments to allow investigators to bring transformative therapies in a more streamlined fashion to patients."

Question. Is our regulatory framework equipped to keep up with gene editing?

Answer. In short: yes. FDA already possesses a robust but flexible regulatory framework that has worked well overseeing biotechnology products for over forty years, including nearly thirty years of gene therapy experience and several recent years with genome editing technologies. From a company perspective, the tools that Congress has provided in Breakthrough Therapy and Regenerative Medicine Advanced Therapy (RMAT) designations are positive developments that, when applied to genome editing products, would allow novel, innovative medicines to access FDA's expedited review programs. We believe FDA will continue to implement the law consistent with congressional intent to assure that highly promising advances, like gene editing products, will qualify and benefit from these important programs.

Thus far, FDA has also taken initiative staying informed of advances in genome editing and has thoughtfully reached out and collaborated with both industry and leading academic centers alike. These efforts have helped to ensure the Agency continues to understand the State of the science in this fast-moving field. The leadership at CBER and the Center's new Office of Tissues and Advanced Therapies have done a commendable job in this regard.

We believe it would be particularly important for the Committee to support and encourage FDA's stakeholder engagement and scientific exchange with researchers in the field. It will be critical, as the science and technology of our field advance, for FDA to sustain this dialog through regular and structured fora with universities, leading specialty societies like the American Society of Gene & Cell Therapy (ASGCT), and industry groups like BIO.

2. In Colorado, there are researchers at our universities using gene editing, specifically CRISPR to cure difficult conditions. At CSU, they are using the technology to delete the HIV genome from infected cells in order to cure the cells and ultimately get rid of the disease.

Question A. How is academia currently aligned with industry to maximize the progress we are seeing in gene editing?

Answer. Genome editing technologies are widely used in research at academic institutions and universities, and there is very strong alignment between these centers and leading biotechnology companies. Our own company has many active collaborations underway with researchers at academic institutions. We view these collaborations as being critically important to our efforts to translate the very promising technology and science of genome editing into medicines for patients.

Question B. What else can we do to stimulate genome editing research in academia?

Answer. We believe that this field is already flourishing, both in the United States and around the globe. Genome editing technologies are widely used in research at academic institutions and universities. Additionally, as Dr. Porteus noted during the Committee's hearing on gene editing, even high school students "are so engaged in this technology, not only about the science, but they love to talk about how it should be applied—the very same issues that all of us in the room are quite interested in, and it's really exciting to see."

Question C. Are there steps we need to take to harmonize efforts internationally?

Answer. Continuing to encourage international harmonization broadly is certainly helpful to the field of biotechnology. As it relates to genome editing, international regulators are building off of thirty years of gene therapy experience, and as a result the U.S. in particular has a robust and flexible regulatory system in place. Nonetheless, in our view it will be critical that regulators continue engaging in professional dialog and exchange with leaders in the genome editing field. The EMA recently convened a meeting for this purpose, and we hope the FDA continues to do so as well.

Question D. How can we further support the progress that academia is making in genome editing?

Answer. Ensuring that research funding for genome editing remains available through NIH, or even increasing that funding, would certainly benefit researchers in the genome editing field. Additionally, we encourage the Committee to seek a statement from the National Institutes of Health (NIH) regarding the totality of its intramural and extramural research funding for genome editing technology, and any recommendations that Dr. Collins, the NIH director, would have to augment or better prioritize these investments. Last, we would also recommend that the Committee explore opportunities for NIH and FDA to coordinate outreach to universities, researchers, innovative companies, clinicians and patients, to maintain the ongoing dialog on genome editing technology and ongoing technical developments, and determine whether cross-cutting, multi-sectoral engagement by both agencies could be formalized on a systematic, ongoing basis.

SENATOR WHITEHOUSE

1. The National Academy of Sciences/National Academy of Medicine report on gene editing discussed the challenges that remain in minimizing unintended results, or "off-target effects," when gene therapy is administered to patients. The National Academies report concluded that there is "no single acceptable off-target rate," and that the acceptable amount of unintended effects will depend on the situation.

Question. In your work, how do you assess the off-target effects of a therapy, and what criteria do you use to weigh the benefits of a therapy versus the costs of its off-target effects?

Answer. Our goal is to make CRISPR medicines with a favorable risk-benefit profile, and one part of how we think about this has to do with our CRISPR molecules' specificity: their observed performance exclusively editing a targeted DNA sequence. We have published extensively on our approaches to improving specificity and have demonstrated that we can make CRISPR molecules with no detectable off-target effects. Other important factors affecting risk-benefit assessments include disease severity and unmet medical need. As each of these will vary depending on the disease, risk-benefit assessments will need to occur on a case-by-case basis.

In this regard, we are confident that the FDA is equipped to evaluate the risks, benefits, safety and efficacy of CRISPR medicines, and look forward to working with them closely.

2. Gene editing technologies like CRISPR hold incredible potential for treating or even curing diseases for which there are currently no available therapies.

Question A. Given this potential, is gene editing research currently receiving adequate Federal support?

Answer. While we are not familiar with the details of the NIH budget as it relates to genome editing support, we do believe robust NIH funding can play an important role in advancing cutting-edge scientific advances. This includes robust funding of genome editing programs at the NIH.

Question B. Would additional Federal investment help spur advancements in gene editing technologies, and if so, what specific areas of research would you like to see additional investment in?

Answer. Ensuring that research funding for genome editing remains available through NIH, or even increasing that funding, would certainly benefit researchers in the genome editing field. Additionally, we encourage the Committee to seek a statement from the National Institutes of Health (NIH) regarding the totality of its intramural and extramural research funding for genome editing technology, and any recommendations that Dr. Collins, the NIH director, would have to augment or better prioritize these investments. Last, we would also recommend that the Committee explore opportunities for NIH and FDA to coordinate outreach to universities, researchers, innovative companies, clinicians and patients, to maintain the ongoing dialog on genome editing technology and ongoing technical developments, and determine whether cross-cutting, multi-sectoral engagement by both agencies could be formalized on a systematic, ongoing basis.

3. In the 2016 Worldwide Threat Assessment of the U.S. Intelligence Community, former Director of National Intelligence James Clapper included gene editing as a potential weapon of mass destruction and proliferation, stating, "Given the broad distribution, low cost, and accelerated pace of development. its deliberate or unintentional misuse might lead to far-reaching economic and national security implications."

Question A. How far is gene editing technology from posing a serious national security threat?

Answer. While it can be conceived in the broadest sense, applications for bioterrorism are beyond the scope of our expertise at Editas Medicine. What we can speak to is the tremendous potential of genome editing technology to advance human health in the years ahead. Should the Committee wish to explore potential national security issues further, it would be our pleasure to reach out to our scientific founders and other third-party groups (such as BIO) to facilitate additional learnings in this area.

Question B. What steps can the United States take now to reduce the potential threat of the misuse of gene editing technology?

Answer. While it can be conceived in the broadest sense, applications for bioterrorism are beyond the scope of our expertise at Editas Medicine. What we can speak to is the tremendous potential of genome editing technology to advance human health in the years ahead. Should the Committee wish to explore potential national security issues further, it would be our pleasure to reach out to our scientific founders and other third-party groups (such as BIO) to facilitate additional learnings in this area.

[Whereupon, at 11:24 a.m., the hearing was adjourned.]