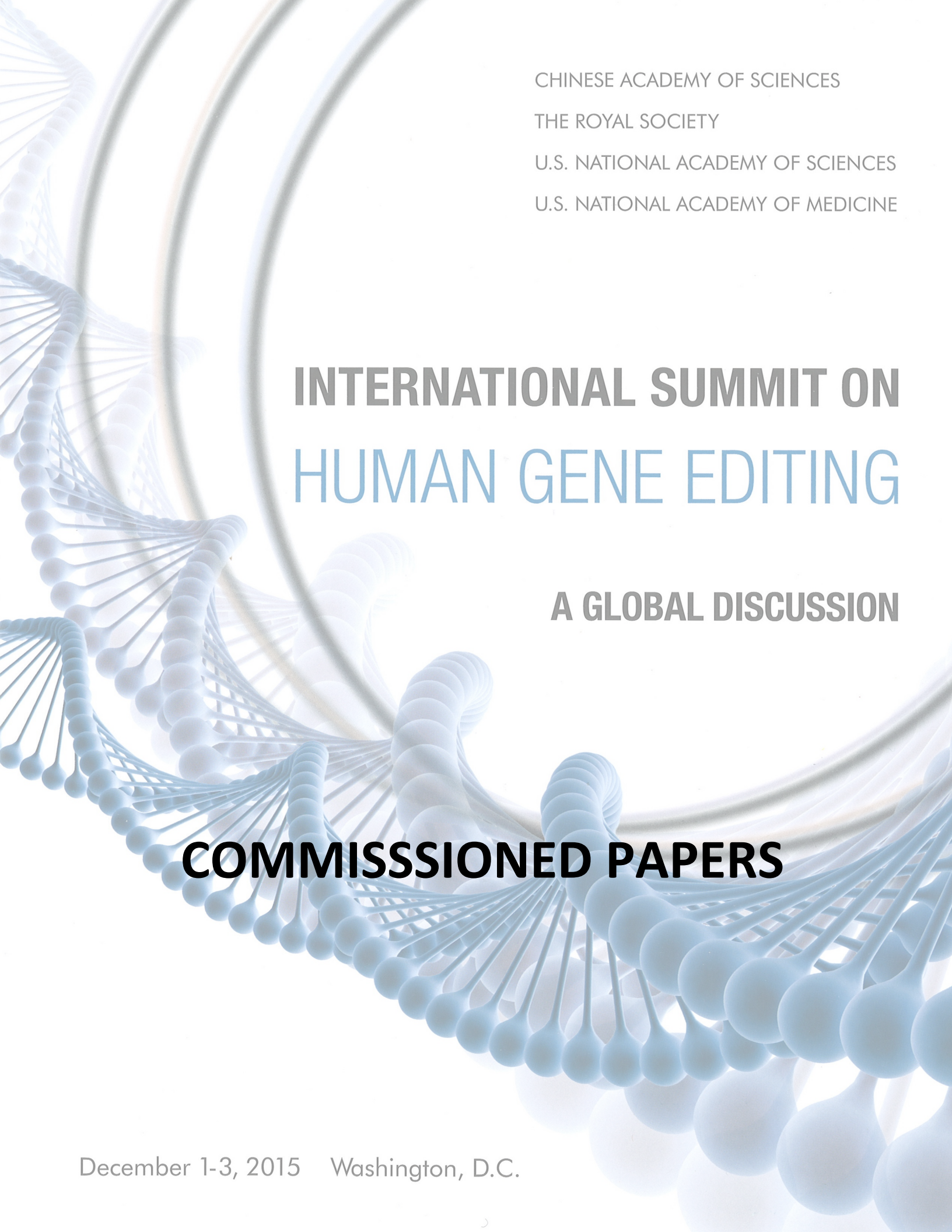

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INTERNATIONAL SUMMIT ON HUMAN GENE EDITING

A GLOBAL DISCUSSION

COMMISSSIONED PAPERS

December 1-3, 2015 Washington, D.C.

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Thanks to the National Institutes of Health, Burroughs Wellcome Fund, Wellcome Trust, and the W.K. Kellogg Foundation Fund for their support of the Summit.

ISMAIL SERAGELDIN, BIBLIOTHECA ALEXANDRIA
THE HISTORICAL CONTEXT

It is a great honor to stand here in the historic building of the National Academy of Sciences at the start of this important summit. I am very happy to be amidst so many distinguished colleagues. I do not doubt that anyone, even for an instant, questions the importance and the legitimacy of the pursuit of knowledge for its own sake or the ethical positions that drive so many of us to seek to feed the hungry, cure the sick, or to protect the environment.

There are moments in history when new scientific developments open the doors to the applications of new technologies to vast new domains full of promise--and full of potential perils, as well, at least in the views of large segments of the population.

Of course, since the very beginning of time, from fire and the kitchen knife, new technologies have always had the potential to do great good and great harm. Humanity has invariably been better served by the pursuit of science than to give into fear. Nevertheless, let us remember that not everything that is technically feasible is ethically desirable.

Literature from Icarus to Frankenstein gives us the image of disasters following in the steps of the hubris of scientists who wanted to play God. But you must recognize that we have been playing God ever since we domesticated plants and animals. We do so every time we turn on the lights and turn night into day.

But more relevant perhaps is to remember Aldous Huxley's *Brave New World* and to reflect on the dark chapters of our history when eugenics and racism combined with disastrous results. We need knowledge, but we also need wisdom.

Also a century ago, the poet T.S. Eliot asked, "Where is the life we have lost in living? Where is the wisdom we have lost in knowledge? Where is the knowledge we have lost in information?" His questions are made even more timely today by the explosion of information made available by new technology, with its accompanying threats to privacy and security, but does anyone really doubt that we are infinitely better off with the internet than without it?

It is up to us to explore and to seek understanding, all the while honing our ethical thinking to deal with the new and unexpected results of research, which could take us down slippery slopes into unintended consequences. We must be armed with a sense of history, a sense of ethics, and an all-consuming curiosity that pushes us to find the newest piece of information and the next and the one after that. Modern science is truly Protean in its imagination and far-reaching in its grasp.

The value of our research today increasingly lies in the fecundity of the questions it throws up and not in the finality of the answers that it provides. Let us welcome this exploration into the new, remaining open to the wildest ideas. Indeed, over 800 years ago, the Egyptian scientist Ibn Al-Nafis said, "When hearing something unusual, do not preemptively reject it, for that would be folly. Indeed, horrible things may turn out to be true. Familiar things may prove to be lies. Truth is truth unto itself, not because many people think it should be so." Even before him, Ibn Al-Haitham in the 10th century told us to accept only that which is supported by evidence and logic, a good basis to start the discussion.

There is no limit to human imagination and ingenuity. The future is truly open-ended. Ethics and public understanding are important to help our societies better cope with the rapidly

changing technological scene, that we need to combine the knowledge of the natural sciences, the insight of the social sciences, and the wisdom of the humanities.

When we explore the new landscape before us with these combined lenses, we may see application in a different light and with a new eye. Again in the words of T.S. Eliot, "We shall not cease from exploration. The end of all of our exploring will be to arrive where we started and know the place for the first time."

Today is such a moment where we are perhaps on the verge of applying this new technology to many domains that hold great promise. As David Baltimore said, we must discuss when and where and how should this technology be applied to humans.

DAVID BALTIMORE, CALIFORNIA INSTITUTE OF TECHNOLOGY
THE PURPOSE OF THE SUMMIT

In 1981, Matthew Meselson pointed out that the puzzle brought to light by Darwin, of what constitutes our heredity, was solved in two tranches. The first lasted from 1900, when Mendel's work of the last half of the 19th century came into the consciousness of the scientific community. It lasted until 1950 or so, when the rules of genetic inheritance had been firmly established.

We then entered a new world of molecular genetics, learning first the chemistry of the underlying molecules of inheritance. Once we knew the chemistry and the topology of the DNA molecule, we learned how to cut it and how to paste it. That resulted in the recombinant DNA revolution of the mid-1970s.

We also learned how to modify DNA in the chromosomes of experimental animals. Those methods remained cumbersome and imperfect, and extending them to human beings was initially unthinkable. Over the years, however, the unthinkable has become conceivable. Today, we sense that we are close to being able to alter human hereditary. Now we must face the questions that arise. How, if at all, do we as a society want to use this capability? That is the question that has motivated this meeting.

Thus, we are here as part of a historical process that dates from Darwin and Mendel's work in the 19th century. We are taking on a heavy responsibility for our society because we understand that we could be on the cusp of a new era in human history. Although gene editing is in its infancy today, it is likely that the pressure to use gene editing will increase with time, and the actions we take now will guide us into the future.

We should remember that there is a larger context for our deliberations. Aldous Huxley in his book *Brave New World* imagined a society built on selection of people to fill particular roles in society, with environmental manipulation to control the social mobility and behavior of the population. That book was written in 1932. He couldn't have conceived of gene editing, but the warning implicit in his book is one that we should take to heart as we face the prospect of this new and powerful means to control the nature of the human population.

Thus, we are initiating a process of taking responsibility for technology with far-ranging implications. The process of accepting this challenge began in January, 2015, when concerns about the consequences of modifying human genomes prompted a small group of scientists and ethicists to convene a meeting in Napa, California. That group recognized the opportunity that genome engineering technology presented to cure genetic disease in humans. It realized that these methods provide the opportunity to reshape elements of the biosphere, providing benefit to the environment and to human society.

Although these new technologies offer unprecedented opportunities for advancing science and treating disease, the group recognized that these technologies might be used prematurely or in ways that might be viewed as inappropriate. Because of these concerns, those at the Napa meeting offered a number of recommendations and called for an international dialogue to further consider the attendant ethical, social, and legal implications of using germline modification techniques.

This summit is a direct response to that call. The Summit planning committee was appointed by the U.S. National Academy of Sciences (NAS) and National Academy of Medicine

(NAM). It is being co-convened with the Chinese Academy of Sciences and the UK's Royal Society.

When the committee began planning this meeting, initial deliberations focused on defining the parameters of the discussion. We recognized that the application of gene editing techniques is not limited to humans. Such technologies can and are already being used to make genetic modifications in non-human organisms. The use of gene editing technologies to alter plants and animals raises many ethical and societal issues that are in and of themselves worthy of careful consideration.

We decided that to maintain focus, to avoid the discussion becoming too diffuse, we needed to limit the conversation to when and whether to proceed with conscious modification of the human genome. We believe that the tactical, clinical, ethical, legal, and social issues relating to the potential to make genetic changes that can be passed on to future generations were sufficiently complex to be a worthy target for a three-day meeting.

The committee was also aware that there are numerous relevant concurrent projects under way, both within the U.S. National Academies and in the larger community of stakeholders. These include two U.S. National Academies studies, one on gene drive in non-human organisms and the other on genetic modification of eggs and zygotes for the prevention of mitochondrial disease.

The planning committee believed that the key was to develop an agenda that gave voice to perspectives not represented in these other activities. As NAM president Victor Dzau has reminded us, there will also be a U.S. National Academies study of germline genetic modification over the next year that will provide a written assessment of the state of the art.

The organizing committee from the start recognized that modern science is a global enterprise and that gene editing technologies are available to and are in use by researchers around the world. Furthermore, different cultures are likely to approach the question of human genome editing from different perspectives. The voices of diverse cultures should be heard at the Summit.

Equally important, consideration of the path forward is not solely the responsibility of scientific researchers. The conversation must incorporate a broad range of stakeholders, including individuals from the bioethics community and social science community, along with specialists in medicine, regulatory affairs, and public policy, as well as of course the lay public.

Thus, we have attempted to include in the agenda participants coming from many perspectives and many nations. We hope that over the next three days, those of you here in Washington and those of you watching online will contribute to what we envision as a global discussion.

The organizing committee also believes that this Summit should be seen as an opportunity to launch a much broader public discussion. The Summit is part of a larger effort to inform policymakers and the public about recent advances. Although powerful new gene editing technologies, such as CRISPR-Cas9, hold great promise, they also raise concerns and present complex challenges.

By holding this meeting, we are saying that this is something to which all people should pay attention. Some might consider that to be fear mongering, but we hope that most will see it as the responsible acceptance of the National Academies' role as expert advisors to the public.

In 1975, I had the privilege of participating in the Asilomar conference on recombinant DNA. That meeting was organized to "review scientific progress in research on recombinant DNA molecules and to discuss appropriate ways in deal with the potential biohazards of this work."

In 1975, as today, we believed that it was prudent to consider the implications of a particular remarkable achievement in science. Then as now, we recognized that we had a responsibility to include a broad community in our discussion. A lot has changed since 1975.

Science has become an increasingly global enterprise. The public has become ever more aware of the power of science and seen the remarkable rate of societal change that can be brought on by the application of new science.

The public has witnessed the huge benefits of basic and medical research, but it is questioning whether these benefits bring attendant modifications of nature that require controls. The public also has become more engaged in debates about science and scientific progress. The new modes of rapid communication have provided novel platforms for these discussions.

At Asilomar, the press participated with the understanding that nothing would be written about what was said until the meeting was concluded. Today, individuals will blog, tweet, and retweet messages about our discussions from within this very room and in real time. Thus, our conversations will be widely disseminated, giving rise to real-time commentary.

This Summit will have many themes and many perspectives, but the overriding question is when, if ever, will we want to use gene editing to change human inheritance. When will it be safe to use it? When will it be therapeutically justified to use it? And a more difficult question, when will we be prepared to say that we are justified to use editing for genetic enhancement purposes?

These are deep and disturbing questions that we hope will be illuminated by this meeting. This Summit will not be the last word on human gene editing. Rather, we hope that our discussions here will serve as a foundation for a meaningful and ongoing global dialogue.

KLAUS RAJEWSKY, MAX DELBRÜCK CENTER FOR MOLECULAR MEDICINE
THE HISTORICAL SCIENTIFIC CONTEXT

Human interest in genetic improvement has a very long history. For example, in the Book of Genesis in the Bible there is a reference to how Jacob made his riches by selecting the strongest and most vigorous little sheep from the weaker ones to breed his herd. But the foundation of modern genetics was laid in 1866 by Gregor Mendel's discovery of the inheritance of specific traits and their segregation in germ cells. This insight was at the time not understood and was completely ignored. There followed a long period of scientific development during which, among other things, chromosomes in cells were discovered and their relevance for heredity later recognized.

Then in 1900, Hugo de Vries, Karl Ehrich Correns, and Ehrich von Tschermak rediscovered Mendel's laws of inheritance, which had been published in the Verhandlungen des naturforschenden Vereines in Brünn, 1865. Almost at the same time, Hugo De Vries was recognizing that gene mutations were probably the drivers of evolution. That was of course followed by the famous work in the United States in the Morgan laboratory.

A next crucial step was the demonstration by Oswald Avery and colleagues at Rockefeller University that DNA was the carrier of inherited genetic information. Finally, in 1953 the DNA double helix was discovered by James Watson and Francis Crick. That started off another revolution by explaining how genetic material can duplicate during cell division.

Then, after the discovery of the genetic triplet code, which governs the translation of the genetic material into proteins, the workhorses of the cell, and the basic rules of the control of gene expression, recombinant DNA technology, mapping and sequencing of genes and genomes, transgenesis—the exchange of genetic material between cells and species—followed.

Finally, from 1984 to 2003, the human genome project led to the sequencing of the entire human genome—not the entire genome actually, but a large part of it. That puts us now in a unique position in that we now understand what Mendel called "cell elements" at the molecular level, not only in the human, but also in many other species

That all happened within 150 years. It is a really breathtaking development. I want to review some of its basics. The human genome is a 2-meter DNA filament organized into chromosomes in the cell nucleus and encoding about 25,000 genes. The central tenet of molecular biology, the so-called central dogma, is a process that starts from the DNA, the double helix, which is composed of a long sequence of pairs of chemical bases (adenine (A), thymine (T), cytosine (C), and guanine (G)) on a sugar-phosphate backbone. The order of A/T and C/G base pairs determines through a triplet code the order of amino acids in the protein encoded by a gene in the DNA. This process of translation of base sequence into amino acid sequence involves initial transcription of DNA into complementary RNA and subsequent translation of the latter into the sequence of amino acids in protein.

A few words about genes and gene expression. Each cell or organism contains a complete genome, but different cell types express different patterns of genes, depending on control elements in the DNA. The function of cells depends on an intact pattern of protein expression.

Furthermore, mutations in genes change the base sequence of the genes or control elements regulating their expression. Mutations can occur spontaneously or be caused by environmental cues. Very importantly, most mutations are repaired by the cells spontaneously.

Insufficient repair will lead to serious problems such as cell damage, cancer, and inherited diseases. Just one word about inherited diseases. Inherited diseases are caused by gene mutations. They are transmitted through the germline from generation to generation. Very importantly, inherited diseases can be monogenic, caused by one particular gene mutation, but in most cases diseases are polygenic in nature and therefore much more difficult to analyze genetically than one might have anticipated.

The central issue is how can genes be intentionally changed to add a desirable trait or eliminate an undesirable one. First, how can we find the gene we want to change in the genome? If one knows the base sequence of the gene in question, one can find this sequence by a complementary sequence, which would pair with the original sequence of the gene.

We can thus construct what one calls a targeting vector, a piece of DNA that is complementary to the gene in the genome that we want to change. Upon introduction of the vector into the cell, these two sequences will find each other. If we are lucky, a process called genetic recombination will subsequently happen: A disease-causing gene can be edited such that it would not cause the disease anymore.

That is what led Oliver Smithies, Mario Capecchi, and Martin Evans in the 1980s to what is called classical gene targeting in mice. Embryonic stem (ES) cells were used in these experiments. These are totipotent cells from an early embryonic stage, the blastocyst. They can be grown in cell culture indefinitely and can be reintroduced into blastocysts to participate in mouse development.

ES cells can be mutated by the gene targeting approach described above. The mutant ES cells are selected, injected into a blastocyst. This is transplanted into a foster mother. Mice are born, crossed, and the mutation is ultimately transmitted into the mouse germline.

This new technology led to a revolution in mouse genetics at the time. Hundreds, thousands of mutant mouse strains were generated. A variation of the technique was developed, called recombinase-assisted targeted mutagenesis and conditional gene targeting, which is more refined. It uses a bacteriophage-derived enzyme, Cre recombinase, which is able to cut out DNA between two short target sequences, called loxP, and leave behind a deletion. It was shown by Brian Sauer that this system could be introduced into mouse cells and would work in the mouse; and Heiner Westphal and Jamey Marth used this technology for the conditional targeting of transgenes.

At the end, here was the scenario for the conditional targeting of genomic genes, something we called the Cre Zoo at that time. The Zoo consisted of a large number of transgenic mice, which expressed Cre transgenes under various kinds of cell type specific control. By crossing these mice to mice in which a genomic target gene of interest was flanked by loxP sites, but otherwise intact, the target gene could be deleted (“knocked-out”) selectively in any desired cell type or at any developmental stage! Further refinements allowed conditional gene activation or the introduction of specific mutations instead of just gene knock-outs.

This led to a situation where one could intentionally edit genes in somatic cells in vivo. Indeed, nowadays there exist hundreds of Cre transgenic mouse lines and mouse lines carrying

conditional alleles of almost any genomic gene. When intercrossed, these lines can be used to target genes, mutate genes, repair genes specifically in particular cell types in vivo.

Altogether this was fantastic progress and opened a huge new field of research. But there was one problem, which actually brings me right into the context of this particular meeting. That is that the generation of mutant alleles in ES and other cells was very inefficient because of the low frequency of spontaneous recombination.

Then came a key observation by Barbara Hohn and Maria Jasin. In higher cells, as had earlier already been seen in yeast, the rate of recombination can be dramatically increased by the introduction of a DNA break into the target gene.

Here is how it works: If one introduces a DNA break into a gene, then the cell tries everything it can to repair this break. It can do so in two fundamentally different ways. It can either use a reaction called non-homologous end-joining (NHEJ), which is just inserting some base pairs in order to save the continuity of the DNA filament. That usually leads to gene inactivation, thus inactivating mutations.

But the cell can also use a repair pathway called homology-directed repair (HDR), where the break is repaired by integration of an available DNA donor template. If one offers the cell that is trying to repair a targeted DNA break a tailored repair template, a tailored mutation can be introduced. This could be used for gene repair. Thus, depending on the repair pathway, one could either achieve gene inactivation by NHEJ, or gene correction through HDR, providing a suitable donor template, which would be recombined into the target gene.

All this looks spectacular and promising for efficient gene editing, and so since the late 1990s there was an intensive search for naturally occurring or engineered sequence-specific DNA nucleases. A number of such enzymes, such as Meganucleases, Zinc finger nucleases and Tale nucleases, became available and became useful tools for gene editing.

But then came the advent of CRISPR/Cas9. Now, I will not go into the CRISPR/Cas9 system in any detail, because you will learn everything about it during the conference. Let me just say that the principle of that system is a DNA endonuclease, Cas9, which is associated with a guide RNA that docks the nuclease to a target gene through base complementarity. One can manipulate the system by manipulating the guide RNA to target any gene in the genome. The RNA is complementary to the target gene. That brings the nuclease to the target gene. A DNA break is introduced. The break can be repaired through gene inactivation or homology directed repair.

This new experimental system is so overwhelmingly efficient and specific that it is changing our entire outlook for future gene editing. Here is the question: What are we going to do with this amazing technology? It can be used in any organism, any cell type in humans—stem cells, induced pluripotent stem cells, embryos perhaps.

This conference will show the amazing extent to which we are becoming masters in the art of manipulating genes in the human. However, our understanding of the function of those genes, and in particular their interactions, is far more limited. It is in fact very limited. That gap is what we will have to deal with.

DANIEL J. KEVLES, NEW YORK UNIVERSITY

THE HISTORY OF EUGENICS*

The human race today stands at a threshold unlike any in the past: It now possesses tools to reshape its own hereditary capacities, perhaps even to realize the dream of eugenicists that human beings might take charge of their own evolution. Over a long time, CRISPR could change the future of humanity, but no one is rushing into it. As we heard earlier today, President Barack Obama's science adviser, John Holdren said human germline editing "is a line that should not be crossed at this time." The question is, will anyone be able to police that line? We are living in the age of biocapitalism, and it is entirely possible that commercial and consumer interests could find a way around the current commitments and controls of governments.

That is an ironic outcome. As anyone who lived in the 20th century knows, "eugenics" is a dirty word largely because of its association with abusive governments, particularly the Nazis, but also as a result of race-improvement policies here in the United States. Politically, it's an untouchable third rail. But scientifically it's now far more plausible than it ever was. With the advent of a new way to modify humans—by transforming their genes, rather than through breeding and extermination—it's not overly alarmist to say eugenics, or whatever we call it this time, could come back, only in a new, private form shaped by the dynamics of democratic consumer culture.

What could happen now is likely to be far more bottom-up than the top-down, state-directed racial programs of the past. We could see individuals and families choosing to edit their genes, whether to prevent illness or improve capacity or looks, and finding themselves encouraged to do so by what was absent in the era of eugenics: the biotechnology industry. Politicians are largely unaware of this possibility, but before long they're going to have to take notice, especially if public demand starts to produce gene-editing services willy-nilly, perhaps at offshore clinics.

Examining why the dream of human biological improvement foundered in the past may help us understand why it may gain support in the future. The dream originated a century and a half ago with the British scientist and explorer Francis Galton, a younger first cousin of Charles Darwin's. It was Galton who dubbed the idea "eugenics," a word he took from the Greek root meaning "good in birth" or "noble in heredity." It was well known that by careful selection farmers and flower fanciers could obtain permanent breeds of plants and animals strong in particular traits. Galton, who believed that not only physical features but mental and moral capacities were inherited, wondered, "Could not the race of men be similarly improved?"

After the turn of the 20th century, Galton's ideas coalesced into a broadly popular movement that enlisted the new science of genetics and attracted the support of such luminaries as Teddy Roosevelt and Supreme Court Justice Oliver Wendell Holmes. They aimed, as Galton had said, to multiply society's "desirables" and get rid of its "undesirables."

A key problem was the difficulty of finding noncoercive means of multiplying the desirables. Galton proposed that the state sponsor competitive examinations in hereditary merit, celebrate the blushing winners in public ceremony, foster wedded unions among them at Westminster Abbey, and encourage by postnatal grants the spawning of numerous eugenically golden offspring. But only the Nazis were willing in practice to enlist the state, establishing

subsidies to racially meritorious couples in proportion to the number of children they bore. Heinrich Himmler urged members of the SS to father numerous children with racially preferred women, and in 1936 he instituted the Lebensborn—spa-like homes where SS mothers, married and unmarried, might receive the best medical care during their confinements.

Human improvers in the United States and Britain followed the route of voluntarism. Eugenics sympathizers such as Teddy Roosevelt, worried by the declining birth rate among their class, urged their women to bear more children for the good of the race. During the 1920s, taking a leaf from Galton's book, they sponsored Fitter Family competitions in the "human stock" section of state agricultural fairs. At the 1924 Kansas Free Fair, winning families in the three categories—small, average and large—were awarded a Governor's Fitter Family Trophy. It is hard to know what made these families stand out as fit, but an indicator is supplied by the fact that all entrants had to take an IQ test—and the Wasserman test for syphilis.

Yet social-radical eugenicists, of whom there were a number on both sides of the Atlantic, were impatient with measures that sought to achieve human improvement within the constraints of conventional marriage and conception. A towering figure among them was J.B.S. Haldane, a brilliant British geneticist and evolutionary theorist. In 1924, in a slim book titled *Daedalus*, he laid out a method for producing human biological improvement that went far beyond urging high-class people to have more babies and behave well. The method centered on "ectogenesis"—the conception and nurturing of fetuses in glass vessels using gametes selected from a small number of superior men and women. Haldane predicted that the resulting offspring would be "so undoubtedly superior to the average that the advance in each generation in any single respect, from the increased output of first-class music to the decreased convictions for theft, is very startling."

Aldous Huxley brilliantly spelled out the dystopian potential of Haldane's scheme in *Brave New World*. But Herman J. Muller joined with a collaborator in Britain named Herbert Brewer to agitate for the realization of Haldane's goal by the use of artificial insemination.

Brewer was a scientifically self-educated postman and Muller an innovative experimental geneticist who would eventually win a Nobel Prize. Both men held, as Brewer put it, that if the salvation of the human species required socialism "to make a better world to live in," it also required eugenics "to make better men to live in the world." Both men fastened on artificial insemination to achieve that purpose because, although it was an imperfectly reliable technology, it was being used successfully with animals, was making headway among women, and took advantage of the fact that men produced millions of times more sperm than women produced eggs. It would thus enable a small number of superior men annually to father thousands of comparable children.

In his 1935 book *Out of the Night*, Muller declared that "in the course of a paltry century or two...it would be possible for the majority of the population to become of the innate quality of such men as Lenin, Newton, Leonardo, Pasteur, Beethoven, Omar Khayyám, Pushkin, Sun Yat-sen…or even to possess their varied faculties combined." Would thousands of women willingly make themselves vessels for the sperm of great men? Assuredly yes! both Muller and Brewer predicted. Muller confidently explained: "How many women, in an enlightened community devoid of superstitious taboos and of sex slavery, would be eager and proud to bear and rear a child of Lenin or of Darwin! Is it not obvious that restraint, rather than compulsion, would be called for?"

What proved obvious was the opposite. Muller and Brewer were naïve in assuming that thousands of women would break out of the day's conventional child-bearing practices and standards.

Ultimately the dreams of all the eugencists went awry for a variety of reasons—not least because of increasingly controversial efforts by governments to get rid of the undesirables from the top down. Many U.S. states enacted laws authorizing compulsory sterilization of people considered unworthy and sterilized some 36,000 hapless victims by 1941. The Nazis went much further, subjecting several hundred thousand people to the gonadal knife and eventually herding some six million Jews—their ultimate undesirables—into the death camps.

After World War II, eugenics became a dirty word. Muller, now an anti-eugenicist, revived a version of his and Brewer's idea in 1959, calling it Germinal Choice. Despite Muller's disapproval, a wealthy plastic-eyeglass maker established a sperm bank for Germinal Choice in Southern California to make the gametes of Nobel laureates available to women eager to improve the quality of the gene pool. Few women—only 15 by the mid-1980s—availed themselves of the opportunity.

The voluntarist multiplication of desirables, whether socially conventional or radical, was also problematic for technical and moral reasons. The aim of producing more desirables called on people to invest their reproductive resources in the service of a public good—the quality of what they called "the race" or, as we would say, the population or the gene pool. But by and large people have children to satisfy themselves, not to fuel some Brave New World. Moreover, it was—to say the least—uncertain that the sperm of one of Muller's heroes would produce offspring of comparable powers. And at the time, Haldane's ectogenesis was technically unrealizable; no one knew how to produce test-tube babies. The reliance on artificial insemination was a vexed strategy. It was offensive under prevailing moral standards, which counted artificial insemination by a donor who was not the woman's husband a form of adultery and which stigmatized single women who bore children.

But now just about all sexual and reproductive practices among consenting adults are acceptable, and although no one knows what genes may contribute to exceptional talent, biologists possess precise and increasing knowledge of which ones figure in numerous diseases and disorders. And CRISPR offers the prospect of biological improvement not for the sake of the gene pool but for whatever advantages it offers to consumers. Indeed, perhaps the most potent force driving its use will be consumer demand aimed at achieving the health of individuals ill with a genetic disease or their improvement in succeeding generations.

During the first third of the 20th century hundreds of men and women wrote to the Eugenics Record Office, at Cold Spring Harbor, New York, asking for advice about what kind of children they might produce. In offering advice, eugenic experts had nothing to go on except analyses of family pedigrees for deleterious traits, a strategy fraught with epistemological and prejudicial pitfalls. Still, the demand for advice continued after the post-World War II decline of the eugenics movement, providing a clientele for the increasingly medically oriented service of genetic counseling. The demand was multiplied in the latter half of the century by a series of technical advances that enabled prenatal diagnosis for flaws in a fetus's genes and that, coupled with Roe v. Wade, permitted prospective parents to abort a troubled fetus.

The ability to have a healthy child—or, for infertile couples, to have a child at all—was further amplified by the advent in the late 1970s of in vitro fertilization (IVF)—that is, the

joining of sperm and egg in a Petri dish. Here was Haldane's ectogenesis, only with the insertion of the resulting embryo into a woman's womb. The method was pioneered by the British scientists Patrick Steptoe and Robert Edwards, who first conducted pioneering research—it eventually won a Nobel Prize—on conception and early gestation. At the time, they faced moral condemnation from scientists and ethicists for experimenting with an ultimate child without its consent and for bringing about, in the vein of Haldane, a test-tube-baby eugenics.

They effectively rebutted the warnings of their critics with the birth, on July 25, 1978, of Louise Brown, the world's first test-tube baby, perfectly formed and healthy, a joy to her hitherto infertile mother. But Edwards had predicted that IVF could also be used to check embryos fertilized in a Petri dish for genetic or chromosomal flaws with the aim of implanting one free of them. IVF is now used for that purpose as well as for assisting infertile couples. It is not hard to imagine couples taking the next step—exploiting IVF to modify pre-implantation embryos by replacing a disease gene with a healthy one.

What seemed like a moral or technical issue in the past is—in this society—very likely to become a consumer question of who can afford it. Will parents want to use germ-line modification to enhance a child's genetic endowment? Will they be willing to insert into their embryonic offspring a set of genes—should any such set ever be identified—associated with extraordinary mental, physical, and/or artistic capacities? Conceivably, yes, given what they already do, if they can afford it, to advantage their children through environmental encouragements such as good schools or biomedical interventions such as the administration of human growth hormone. They might readily cross the line between germline medical treatment and enhancement if today's enhancement—say, the ability to do complex computing—turns into an essential capacity, like language, tomorrow.

Whatever purpose they might choose for germ-line editing, the contemporary right to reproductive freedom would assist their pursuit of it. The offspring would not be test-tube products of Huxley's fascist, anti-family Fordism. They would be babies born of women, not conditioned but nurtured as much or as little as any other child. As early as 1989, at the beginning of the Human Genome Project, the journal *Trends in Biotechnology* pointedly noted: "'Human improvement' is a fact of life, not because of the state eugenics committee, but because of consumer demand. How can we expect to deal responsibly with human genetic information in such a culture?"

How indeed, we might further ask amid the increasing commercialization of biomedicine. Biotechnology companies have rapidly embraced CRISPR/Cas9, exploring new ways to treat patients with genetic diseases. If they find methods of safely editing human germlines for medical or enhancement aims, they would likely pressure regulators to permit their use and, as they do with drugs, heavily advertise their availability to consumers.

As Haldane observed in *Daedalus*, biological innovations initially regarded as repugnant tend eventually to become commonplace. Just as it occurred with artificial insemination, so it may happen in the age of biocapitalism with human germline editing.

*A version of this paper originally appeared in *Politico*.

ALTA CHARO, UNIVERSITY OF WISCONSIN, MADISON
THE LEGAL/REGULATORY CONTEXT

My intention is to give a very broad overview of how it is that we look at regulation of biotechnology around the world. We will hear a lot of detail about that later on, on a country-by-country basis. But let me first note that we are not talking only about government when we talk about law and regulation and biotechnology. We are really talking essentially about an ecosystem that is made up not only of government, but also of the public and the private industry that is the producer of innovation based on some of the producers of basic knowledge and applied research coming out of our universities.

The ecology of this system is one in which there is an abundance of different kinds of legal or policy issues that combine to affect how it is that biotechnology is either promoted or hindered in any particular country. It ranges from things such as intellectual property rights that are reflected in areas such as patent policy to international trade laws, which will have a huge effect on whether or not the new products are going to be able to cross borders easily or with great difficulty, and under what kinds of particular conditions. The regulatory framework is going to determine the speed at which biotechnology moves from laboratory to research to marketed product.

Then the consumer demand will also be a profoundly important feature in determining which products actually are developed because so many discoveries really do not lead to something that the public wants or needs, or that it knows it wants and needs. This will also be affected by variables such as stigma and cultural attitudes.

Last of course, but certainly not least, are areas of public research and investment. All of these together are going to combine into a vision of how it is that a particular country moves or does not move biotechnology. Some of the categories that have been proposed by other scholars range from promotional, in which you are actually pushing the innovation, to a more neutral stance in which it simply proceeds or not with as little government direction as possible, to precautionary, to an absolutely prohibitive system that either defunds entirely or even makes criminal the technology.

It is worth keeping in mind that within a country, one can have very different attitudes about different aspects of biotechnology. For example, in the United States, we tend to have a fairly permissive approach to biotechnology as applied to genetically engineered animals and plants in the agricultural sector, whereas we have a much more cautious approach when it comes to these biotechnology in the context of human clinical care and therapies. There does not have to be a single approach to biotechnology across all application areas. They can differ from place to place or within a country.

One can also look at how different areas of policy can be tied to one or another of these visions of an overall biotechnology direction. For example, full patent protection, strong patent protection can be viewed as promotional because it gives industry the greatest possible financial incentive to pursue their particular application areas. However, from the basic science and research community point of view, strong patent protection can sometimes be perceived as slowing the ability to collaborate or take advantage of one another's work. It has a mixed effect.

In the area of biosafety, obviously if there is very little careful screening, one is going to be able to move applications out more quickly. At the far end, of course, there is the assumption that all applications are dangerous, and they are absolutely prohibited. In between are the permissive and precautionary kinds of stances. We see more case-by-case evaluation of biotechnology products where everything really begins to hinge simply on the presumption about risk.

Do you presume it is dangerous until it is proven safe, in which case you have a precautionary approach? Or do you presume it is safe until it is proven dangerous, which is a much more permissive approach? Since it is often impossible to prove either danger or safety, where that presumption falls will often be more determinative than anything else in your system about how quickly things move from basic science laboratory to clinical research to application.

Finally, in the area of public information, there is a very lively debate going on particularly in the United States about the labeling of foods that have some component that involves modern biotechnology. For example, now that the Food and Drug Administration has approved the sale of a genetically modified farmed salmon, does that that salmon have to be identified for consumers.

If we have systems that carefully distinguish between those things that are the products of modern biotechnology and those that aren't, we are setting ourselves up potentially for a more precautionary preventive approach because it will tie into public attitudes, often attitudes that are based on concern about either the corporate influence or about the actual underlying science. If the regulatory distinction is drawn only in the face of actual evidence of difference, of course products move more quickly, and we are in a more kind of promotional stance.

In order to implement any one of these approaches, we have a variety of mechanisms that range from the least to the most enforceable. Public consultation being the least enforceable and moving across the spectrum to regulatory and legislative measures, which could either direct what you can do or what you can get money to do.

In the areas of public consultation, we have got numerous examples from around the world. In the United States the National Environmental Policy Act is unusual among environmental laws because rather than telling individuals or companies what they can and cannot do, it simply provides that when the government makes a particular decision, it must be subjected to a higher degree of public scrutiny than is typical. The catchphrase for this approach is that sunlight is the best disinfectant. By incorporating public comment, it creates political pressure that can drive decisions in one way or another, and it allows for some interplay between government expertise/authority and public consultation. We see other examples of it in the approval process for products such as engineered salmon, which required a number of public hearings.

Canada, when it looked at assisted reproduction across many different forms, formed a royal commission on new reproductive technologies that traveled the country from east to west holding public hearings on the topic. In the European Union (EU), genetically engineered foods, or GMOs as they is usually referred to there, are of special concern. There is actually an EU directive requiring that there be a degree of public access to information whenever a product potentially affects biodiversity or other environmental elements.

Public consultation is considered an alternative to a directive centralized form of governance. One simply creates the situation in which the public can, through its own decentralized processes, exert pressure on government or on industry, and alter the direction or the speed of biotechnology innovation.

Next on this kind of hierarchy of enforceability comes voluntary self-regulation. David Baltimore has already mentioned the 1975 Asilomar conference, which was one of the more notable examples of voluntary self-regulation by the scientific community when it recognized that there were unknowns that needed to be managed before it pushed forward at full speed. It voluntarily imposed on itself either moratoria on certain applications entirely or endorsed and then self-implemented a series of precautionary measures having to do with containment of potentially or possibly dangerous elements. A more recent example is the guidelines for human embryonic stem cell research, which were developed by the U.S. National Academies and the International Society for Stem Cell Research.

What is interesting about these is that unlike the government-imposed rules that we saw in other places, these were truly self-imposed rules that were seriously constraining in many ways. They often called for prohibiting payment for certain kinds of donations and services in ways that really limited the ability of the scientific community to move as quickly as it might want to.

It called for specific limitations on certain kinds of experiments, particularly the use of chimeras. It certainly laid out the conditions by which one would feel comfortable accepting the gametes and the embryos needed for the research.

It was a success in the sense that it forestalled what might have been really onerous government action at the state and even federal level because of the ability of the scientific community to say it had been able to organize itself for self-regulation. It demonstrated it could be more flexible and more nuanced, but also that it could be very responsible. That played a very important role.

Gain of function research is a very awkward name for research that increases the pathogenicity, transmissibility, or resistance to countermeasures of known pathogens. It also has been the subject of self-imposed regulation among the scientific community about either doing certain experiments or publishing all of the details about them.

Interestingly, these kinds of voluntary self-regulatory activities often lead directly into some government adoption by proxy of much of the content of these self-imposed rules. For example, in the gain of function area, some of the self-imposed rules led to a National Academies report, which then led in turn to the creation of the National Scientific Advisory Board for Biosecurity (NSABB), which collaborates with its counterparts across the world to try to manage situations where there is fear that publication of key data will actually facilitate the transformation of useful biotechnology into bioterrorism.

We also have government guidelines and guidances in other areas. These kinds of guidances technically are not enforceable, and yet they are very strongly persuasive because complying with them creates what essentially is a safe haven for companies. They know that if they stay within these guidances, they are not going to run afoul of some actual regulation or law. They also create strong social norms.

At the international level, we have the Counsel for International Organizations of Medical Sciences (CIOMS), which is very influential in trying to create global standards for

human subjects research. It refers back specifically to the Nuremberg protocols. It has the ability to be more restrictive than any particular national set of rules.

That doesn't mean that national laws will necessarily follow. It becomes a kind of goal post in which any deviation from these ideals needs to be justified by some necessity in order to provide for the common good. Therefore, it becomes extremely influential, even if not enforceable.

At the far end of the spectrum, of course, we have regulation and legislation. For example, many nations have laws that specifically ban human cloning, although the United States is not one of them. That is not to say that it actually happens in the United States; it is just that there is no U.S. legislation that explicitly bans it. The U.S. regulatory system could, in theory, approve it, but it has never indicated any particular willingness to do so. Effectively, it is impossible to do legally in the United States. Yet it is not considered a ban.

We should keep in mind that legislation has the advantage of being more politically credible, particularly in more or less functioning democracies, because it is seen as a product of elected representatives. On the other hand, legislation is extremely rigid and difficult to change. Once it is in place, it can be impossible to remove it, and it is often resistant to nuance. Therefore, it can be a very blunt instrument.

Regulation has the ability to be much more responsive, much more detailed, much more influenced by expert information. Yet, it also begins to become somewhat more divorced from public sentiment and begins to move into the world of the administrative state where there is rule by expert, which has its own kinds of challenges for democratic systems.

Let's look briefly at a few activities related more specifically to gene therapy and to germline manipulation. There are international instruments that have been written at various levels to address aspects of genetics. For example, the Counsel of Europe's Oviedo Convention, which says that predictive genetic tests should be used only for medical purposes. It specifically calls for a prohibition on the use of genetic engineering of the germline or changing the makeup of the following generations. It builds on earlier European conventions.

But like many international instruments, it is not ratified by every member country and, even when ratified, does not necessarily get implemented with concrete legislation. It has great normative value and can occasionally have enforcement-level value, but it is often lacking in the latter.

In the United States, gene therapy is handled in a regulatory system that considers it from the point of view of being a biologic and of being effectively something that is akin to a drug or a device depending on its mode of operation. It comes under the comprehensive regulation of the Food and Drug Administration and under the multiple different laws focusing on infection control, as well as on efficacy and safety.

The United States also seeks guidance from advisory bodies such as the Recombinant DNA Advisory Committee (RAC) and the local research subjects review bodies that help to make sure that the human clinical trials are managed in a way that accords with our norms and regulations.

But what is perhaps distinctive about the United States is that although it has very strong controls in the premarket stage of these technologies, once a drug or a device or a biologic is on the market, the control becomes much weaker. That is, the United States regulates the products but not the physicians who actually use those products. Physicians have

the discretion to take a product that was approved for one purpose, and use it for a different purpose, a different population or a different dosage. There are some post-market mechanisms to track the quality of this work and to ratchet it back, but they are not as strong as in other countries.

Gene therapy in Korea is something that actually has a pathway very similar to the one in the United States. Interestingly, Korea has now come to have a focus on innovation, with the expanded access to investigational drugs. It is also developing a system of conditional approval, which would allow for some use of a product prior to the accumulation of the level of evidence that is now required in systems such as that in the United States.

Again, there are different versions of this. Even in the United States, regulators sometimes accept evidence from surrogate markers of effectiveness, which allows for a faster path to marketing. Many other countries are also considering adopting some form of conditional approval.

The United Kingdom's system is a little different because not only is it operating within the context of the European Union (EU) and its directives, but it has its own very strong premarket review process. In addition, it has very strong post-market regulation of any procedures involving embryos or human fertilization. Thus, UK regulations cover not just the product, but also where the product can be used and by whom.

The European Union has also added special provisions for advanced therapy medicinal products. Gene therapy, I think, is going to be among them, so that there is an extra layer of EU review for quality control at a centralized level.

Japan has a regulatory pathway that tries to identify prospectively those things that are going to be high, medium or low risk, and to regulate them accordingly. The United States follows a similar process in its regulation of medical devices.

But for drug regulation, the United States treats everything *ab initio* as equally dangerous and runs every proposed drug through the same paces of testing for safety and efficacy. By contrast, in Japan you will actually see an initial determination about the level of risk that is likely to be present for each proposed drug and the degree of stringency that the regulatory process must apply as a result.

Japan also has this recently added conditional approval pathway specifically for regenerative medicine and gene therapy products. It will be very interesting to see how this operates. It is still very new, so the experience is very limited.

There is certainly some concern that if new products are put into use too early in controversial fields such as embryonic stem cell research or gene therapy, a single high-profile failure might set back the entire field. Certainly in the United States, the death of Jesse Gelsinger at the University of Pennsylvania in a gene therapy trial set back the field by years.

One of the challenges with the conditional therapy pathway is to balance the desire to move these things forward as quickly as possible and at the same time to avoid the kind of adverse outcomes that not only injure those particular individuals but could slow progress to the point where many individuals who could have benefited in the future are denied the technology because it is delayed so significantly.

Singapore also has a risk-based approach like Japan's. What is interesting in Singapore is that it actually tries to figure out what would be in the area of cell therapy a high- versus low-risk kind of intervention. The variables that are used in Singapore include whether the

manipulation is substantial or minimal, whether or not the intended use is homologous or non-homologous, and whether or not this is going to be combined with some drug or some device or some other biologic.

The only thing I might perhaps add is autologous versus non-autologous use. In Singapore, this distinction is used to classify the level of risk. In the United States, it is used to determine if the FDA has jurisdiction at all to regulate that particular product.

Finally, Brazil provides an example of regulation and governance by accretion. It recently approved laws related specifically to genetically-engineered foods and stem cell research and cell therapy, but they are layered on top of earlier, more general rules—constitutional prohibitions on the sale of any kind of human tissue and 1996 laws on patenting of human biological materials—creating a situation of confusion. The result is paralysis while people try to figure out how the laws are going to interact. It is a cautionary tale about how to proceed with legislation against the backdrop of older decisions that may have been made against different imaginary scenarios.

Looking specifically at regulation of human germline modification, a 2014 survey of 39 countries by Araki and Ishii found a variety of regulatory approaches. Many European countries legally prohibit any intervention in the germline. Others countries have advisory guidelines. The United States has a complicated regulatory scheme that would make it very difficult to perform any germline modification. There are also funding restrictions on embryo research that might have a very strong effect on the underlying basic science needed to even get to the point of regulatory approval. And many countries have simply not considered the possibility.

I want to conclude with a few final thoughts. There is a very fundamental divide in the world about how we regulate biotechnology that goes beyond promotional versus permissive versus prohibitive or precautionary. It is whether or not we think of biotechnology as a thing unto itself, or if we think of it simply as one more tool that goes into making various products.

If you regulate the technology, you regulate everything about technology in a comprehensive way. You have an example in the European Union's community strategy. It is easier for the public to understand what is the law on biotechnology. Somebody can point to it and say, that is the law. You can focus on key aspects of the science that create key questions about the effects of a particular kind of innovation. It allows you to have consistent and overarching approaches to questions of great philosophical significance such as what we mean when we say "human dignity" or "genetic heritage of mankind."

It also has the problem of needing much more specific legislation to focus in on the individual products because, as is noted in a contrasting system where you regulate the product and not the technology, as is the case in the United States, the technology itself is neither inherently dangerous nor safe. It is dangerous in some contexts and safe in others. In some products, it is easier to predict its effects. In other products, it is much less likely. Some products may have environmental impacts, and the impact of others will be confined to a single individual or single animal.

Regulating by product gives you the advantage of being able to be much more specific about the degree of risk that you fear or anticipate, and the degree of caution you need, as well as being able to take advantage of mature degrees of expertise in both the regulatory pathways appropriate for drug versus a food, and the expert people who have been implementing those pathways for years.

The trouble is that it can be confusing to the public. If someone asks what is the law on biotechnology, the answer is that there are 19 different laws that cover drugs, devices, agricultural products, livestock, etc. To many people this sounds as if the country is not regulating biotechnology. It creates a real disconnect with public understanding. It certainly creates the possibility for unintended or even unnoticed gaps among these laws or conflicts among them.

Last, whenever we are talking about this, whether in the human or non-human application, but particularly in the human, it is important to think about the issues around where we want to exercise control. The pre-market kind of control is truly important in order to avoid the devastating adverse events that can occur if we move too quickly.

But if the pre-market control is too strong, not only does it slow the technology, but at a business level, it creates a barrier to market entry for smaller players. Mature companies with large staffs know how to maneuver the regulatory system. A small company with very low levels of capital and a high burn rate is not necessarily going to be able to survive long enough to deal with a long and difficult pre-market process.

The AquAdvantage salmon that I mentioned above is made by a company that has repeatedly been on the verge, they say, of bankruptcy during the twenty-some years that the product was undergoing review. Another company in Canada that was trying to produce a pig that would be less environmentally damaging did wind up abandoning this particular activity in part because that pathway was so long, so slow, and so expensive. There is a cost to pre-market controls that are too strong in terms of driving out the small, upstart often very creative innovators in this field.

One thing we have learned is that conditions on research grants, whether from government or philanthropies, can also serve as a strong regulator, but at least this is one that is much more responsive and much easier to adapt quickly to changing circumstances and changing levels of knowledge.

Finally, harmonization across different country lines, which is one of the most important things happening here today, is really crucial. If we want scientists to be able to use one another's materials, they have to have confidence that the materials were derived and managed in a way that meets everybody's common expectations of both ethical and biomedically safe levels of care.

We want to have uniformly high standards for research and therapy. We want to be able to reduce conflicts and redundancies in review procedures if we want the science to proceed in a way that is efficient as well as responsible. We learned this very much with the many conflicts among jurisdictions in the area of embryonic stem cell research.

I may sound like somebody who thinks that innovation and precaution are at odds with one another. I would not like you to leave with that impression. The more that we have effective systems for responsible oversight in the development and deployment of a technology, the more we can take chances. We can move a technology quickly because we have a chance to back up at the end and change course.

From my personal perspective, innovation is not something that is somehow in conflict with precaution. They are complementary strategies in which precaution will facilitate innovation and give us the confidence we need to support these new and risk-taking technologies.

ERIC S. LANDER, BROAD INSTITUTE OF HARVARD AND MIT
WHAT WE DON'T KNOW

My assignment from the organizing committee is to look at the genetic basis of human disease and to ask how does it inform our thinking about germline editing. The first step is to be clear about what diseases we are talking about. I'm going to divide things into two categories for the purpose of this discussion. First, there are rare Mendelian diseases, including relatively well known conditions such as cystic fibrosis and Huntington's disease as well as more than 4,000 little-known conditions that have frequencies that might be 1 in 100,000 or 1 in a million. These conditions are caused by mutations in a single gene. Although genetically very simple, they can have devastating consequences.

Second, we have a large number of common diseases, which are, for the most part, polygenic. These include heart disease, Alzheimer's disease, abd schizophrenia. We have identified genetic factors that play a role in these conditions, but each is only one of many factors that contribute to these conditions, and they are by no means determinative. There is a locus that has a significant effect, although by no means determinative, of Alzheimer's. Likewise, we know that there are many genes in which variations are linked to characteristics such as height or obesity, but we can't isolate or quantify their impact. The situation is more complex with things like 'intelligence' because we don't even have a clear definition of what we mean by intelligence and therefore no reliable way to measure it. Genes play some role, but we cannot specify what it is.

So what do people want to do with this evolving knowledge of genetics? There are a range of aspirations. I hear calls to eliminate all cases of genetic disease. Some people go so far as to say let us not just eliminate the cases of disease, but banish all disease alleles from the human population. That's with regard to these severe Mendelian diseases. With regard to the common genetic diseases, they ask why don't we eliminate or greatly reduce disease risk. And, some say, maybe let's enhance the population, give everybody all the protections that you might wish them to have against all possible diseases, infectious and otherwise. In other words, let's give everyone the best possible genome.

So that's what one hears in public discussions and in the popular media. But the scientific community knows that this speculation is unrealistic. I want to talk about what we actually know about human disease genes, and I will provide a brief overview of the progress of knowledge in the past 30 years.

Sometime in the 1980s, a bunch of very simple principles were laid out as to how we might find the genes for disease. For simple Mendelian diseases, a famous paper by David Botstein and others told us a recipe for mapping the genes for simple Mendelian diseases by studying meaningless spelling differences scattered around the genome and finding some that show the same inheritance pattern as the disease gene.

If two things have a correlated inheritance pattern, they can't be too far away. For example, they might show genetic recombination only 1% of the time. Unfortunately, 1% recombination means that you are still about a million letters of DNA away. So you would still have to plod from a linked genetic marker to find the disease gene. In the case of cystic fibrosis that took about 5 years of work for a whole team, spending tens of millions of dollars to find

that gene. When they did, it turned out to appear to be a boring string of letters—though not boring at all to people with this genetic condition. Researchers found that three letters were deleted in the genetic code of the vast majority of patients who have cystic fibrosis, resulting in the deletion of one amino acid of that protein.

With this information, we could do a genetic test to see who carries the mutation. And, we could ask a computer if it had ever seen any proteins like that before; in fact, the computer came back and said the CF protein looks a lot like proteins that sit in the membrane and transport things: Congratulations, you probably discovered that the cystic fibrosis gene is a transporter!

That was the science, and it is fantastic. It was also very slow, but we will come to that in a second.

Also in the 1980s there were a lot of ideas about how to extend this concept beyond simple single-gene diseases. For example, do we need the families? Maybe we can get away without the families. And for simple diseases, new approaches were developed that don't require families, such as by looking just at inbred individuals who have a recessive genetic disease. These individuals will have a region of the genome that was transmitted on both sides of the family from a common ancestor, and we could recognize this by a bunch of genetic markers in a row that were all homozygous, that is the identifical on both the maternal and paternal chromosomes.

And then we turned to populations such as that of Finland, which started 2,000 years ago with a relatively small founding group. Almost anybody in Finland who has a particular rare genetic disease inherited it from a common ancestor, and we can recognize the chunk of the ancestral chromosome inherited from the common ancestor in almost all the people today who have the disease. So we can map those genes just by looking at the population.

Well, that gave rise to the idea that maybe we could go further. Maybe we could take this concept of mapping disease genes in populations and extend it from places like Finland to larger populations. Finland goes back 2,000 years, but Europe goes back 8,000 years, and other populations go back 10,000 years. With a denser and denser genetic map, we could find the regions of the genome where people who have the disease on average more often share the same spelling differences in a region.

So there were methods developed for mapping diseases based on what we would call common variant association studies. That is, the people who have the disease share certain particular common spellings more often than the people who don't.

More recently, there is the idea that you don't need to look only at common variants. We could just observe that the people who have a disease have a higher frequency of rare mutations in a particular gene than the people who don't have the disease.

Now, to use any of these approaches, we needed a tremendous amount of data and technology. Just for simple Mendelian diseases we needed to have genetic signposts up and down the genome. Then we needed to be able to march along the chromosome and find the disease gene and sequence it.

And well, if we wanted to then apply the common variant methods, we would need to study hundreds of thousands of variants in thousands of people. And, if we wanted to study the rare genetic variants, we couldn't look just at signposts. We'd have to study the entire genome sequence in thousands of people.

So that is exactly what the scientific community did. It got its act together and developed the tools and methods. First was the Human Genome Project. The goal of the Human Genome Project was to find those genetic signposts, connect them together, read out all the sequence, make a list of all the genes, and ensure that all that information is freely and immediately available to anybody wherever they are in academia or industry or in a developed country or developing country.

I will completely skate over the 13-year process of completing the human genome. Suffice it to say: it got done.

So then, of course, having a sequence of one person was not enough. We needed to know virtually all the genetic variation in the entire human population.

So, that happened as well. There were international projects to collect all the genetic variants, and today something like 99.8% of the genetic variants in this audience are already in the databases. So we essentially have all human genetic variation, and we can genotype it really quickly: there are little genotyping chips where we take a little bit of your DNA, wash it over the chip, and read out 2.5 million or 10 million genetic variants.

Moreover, if we actually wanted to do full genomic sequencing, not just the 2 million signposts, to look for even the rarest genetic variants, the costs have dropped so dramatically that this is now feasible. It's about 2 million times cheaper today to do that than when we first did the human genome. That's pretty good for a relatively short time. I don't know anything that has ever dropped 2 million-fold in cost over about a decade.

So it means that now for about $1,500 you can get a genome sequenced. We can actually do all these things that we dreamed about and thought about and developed methods for in the 1980s, using the tools and information that were created in the 1990s and the 2000s.

So what about mapping disease genes? There has been a lot of that that has been going on. The mapping of disease genes—those simple Mendelian disease genes such as cystic fibrosis that used to take so much work—are now almost a piece of cake. It's almost a rotation project for a student to map the location of the disease gene, if you happen to have the samples in hand.

The genetics community knew about 70 disease genes in 1990. By the time the Human Genome Project was completed, it was about 1,700. Today it's about 4,000, and the limitation is just having enough samples to study. Interestingly, though, the family-based mapping for common genetic diseases failed miserably. There was a theory that for common diseases, such as heart disease and Alzheimer's, we map them like Mendelian diseases within families. That approach failed completely. Almost nothing was found that way, because in fact common disease is not just the whole collection of individual rare Mendelian diseases. It has a different genetic architecture.

The handful of exceptions that were found were things like ApoE4 in Alzheimer's and NOD2 in Crohn's disease. These were cases where you had things that were fairly common in the population, not like rare mutations, and they had effect sizes that were modest--two, three, four, fivefold. That suggested that instead of mapping in families, we should look at whole populations—by looking at the frequencies of the common genetic variants and pileups of rare genetic variants.

So folks did that. They took these collections of common genetic variants and they started mapping. The world found very little in 2001, 2002, 2003, 2004. Then as the better

technology and richer information became available, we saw a big uptick in 2005 and larger increases after that. So, today, there are something like 4,000 or 5,000 such discoveries across hundreds of different diseases and traits. We have huge piles of common genetic variants associated with different diseases.

Recently, human geneticists are finding genes with rare genetic variants associated with these diseases. Now I'm not going to go into all of the biology, but I will tell you very quickly one particular story, because it will be relevant to what I want to say about human editing. I am going to relate a story of work by three particular people, Mark Daly, Steve McCarroll, Beth Stevens, all at the Broad, and their collaborators. They are Harvard professors who work on schizophrenia, and their latest research will be coming out in late January. I'm not going to go into the biological details, but I want to give you a sense of what things look like.

Some years ago, they and a bunch of colleagues around the world did a genetic study with 6,000 people with schizophrenia; they looked at 2 million genetic variants in 6,000 people and found absolutely nothing. At least nothing that was statistically significant. That was very depressing.

But they knew that there was something there. They could tell statistically there was some signal there, and so they expanded it to 20,000 people and found five genes. They expanded it to 50,000 people and they found 62 genes, and they expanded it to 110,000 people, and there are now 108 genes associated with schizophrenia. They published these results about a year and a half ago.

Interestingly, they found the genetic signal on chromosome 6 in a region called the HLA complex, which is related to immune reactions to infectious disease. They wanted to figure out what it was. Many people assumed this meant schizophrenia must have something to do with infectious disease.

But you can't tell until you actually look. People had a lot of theories about which infectious disease it was. The *Atlantic* magazine had an article about how you get mental illness from your cat. That was *Toxoplasma gondii*.

So what was the gene? I will just make a very long story, which will be told very thoroughly in the paper, very short to say they found the gene and it's called C4. I will tell you one detail about it. The gene C4 has a 'day job' functioning in the immune system. It is involved in marking microbes for destruction by the immune system.

But that is not the job relevant to schizophrenia. It turns out it also has a 'night job'. The same gene is involved in the brain in marking synapses, connections between nerves, for destruction. It is a gene involved in the pruning of synaptic connections, and the paper shows genetic variants associated with higher expression of C4 confer higher risk of schizophrenia. This strongly suggests that schizophrenia is a disease related, at least in part, to the level of synaptic pruning. That actually fits with some really old neuroanatomical observations, namely that the brains of patients with schizophrenia appear to have fewer synaptic connections, although nobody ever knew whether that was a cause or an effect of having schizophrenia, and also that a tremendous amount of synaptic pruning goes on in late adolescence, which is the time of onset of schizophrenia.

So it is possible, and I think the evidence is now piling up for other reasons, that schizophrenia may turn out to be at least in part a disease of excess synaptic pruning. That presents a therapeutic hypothesis that you can't act on today but might be able to act on at

some point in the future by modulating synaptic pruning in some way.

I raise this not because I want to discuss schizophrenia but to say this is why we do genetic mapping. It points us to biological processes that might lead to treatments. I am going to come back to C4 in a moment.

So let's now turn to the implications for gene editing. Let's start with the rare Mendelian diseases. Let's start with a dominant disease. The vast majority of the time the affected person is a heterozygote. They have one copy, not two copies of the disease-causing variant.

Well, this means that 50 percent of their offspring will inherit that and 50 percent will not. So half of their embryos will be free of that disease. You could use preimplantation genetic diagnostics (PGD) to identify which half is not going to inherit the genetic disease and implant those embryos. It's not immediately clear why you'd want to use gene editing as a fix - selecting those that did get the genetic disease and trying to fix them by gene editing is much more difficult.

Now there is the possibility that we might not have enough embryos that have inherited the healthy gene, but half is pretty big fraction. Still, it is possible to have a situation in which an insufficient number of unaffected embryos are produced. Of course, if the dream of being able to turn somatic cells into germ cells and to culture them, then we wouldn't face this problem because we'd have an unlimited supply.

The challenging case is when an individual is *homozygous* for a dominant disorder, having two copies of the gene. In that case, every one of the offspring will inherit the genetic disease. This is a serious case in which genome editing would be useful. It's also an extremely rare case. Both of those statements are true, and I make no value judgment about them. But I want to emphasize just how rare this is. In the entire scientific literature, the number of instances of Huntington's disease is measured in the dozens worldwide, and for many other diseases it is likely to be lower. So it is very unlikely—although still possible—that an individual would be homozygous for a dominant disease, and this particular individual would really benefit right now from germline editing.

What about recessive diseases? Well, here you have two parents who typically are unaffected. They are heterozygous carriers. They usually don't even *know* that they carry the gene, yet they can have a child who has the genetic disease. Of course, if they do know they carry the disease, they could use PGD: 75% of the embryos would not have the genetic disease. The numbers game is even more in their favor, although it is always possible that they continue to always draw embryos that are homozygous for the disease alleles. However, it is pretty unlikely that that will be the case.

The truth is—and this should be said here—if we really care about helping parents avoid cases of genetic disease, germline editing is not the first, second, third, or fourth thing that we should be thinking about. What we should be thinking about is that the vast majority of people who have children with a recessive disease were never aware they were carriers. Most such recessive disease arises unexpected in a family. The most important thing is to make genetic diagnostics available so they could know they are carriers and be able to avail themselves of PGD. This would be the most effective option both from a societal basis and from helping the largest number of parents. It is important that we think about how we want to deploy our resources here.

In addition, if we wanted to *eliminate* all genetic disease, we would have to do more

than simply eliminate the production of these homozygous embryos. We would have to eliminate the production of heterozygous embryos as well.

I should note that means all of you should not be engaging in natural reproduction, because all of you carry multiple, probably about a dozen, genetic disease genes in the heterozygous state. So if we want to get serious about eliminating all these genetic variants in that might cause disease, it would require everybody's effort to stop reproducing naturally and instead use PGD. I don't think that is very likely to happen.

The case that is most plausible for germline editing is where you have two parents who are homozygotes. Then all the kids are going to inherit the genetic disease. It happens. But, it just isn't very common, because most genetic diseases are exceedingly rare to start with. Many of them are very debilitating. And situations where two parents with the same genetic disease marry and have kids are exceedingly rare. The most likely case I can think of is two parents with congenital deafness due to the same gene. There are actually multiple genes that could cause deafness; if the parents have deafness due to different genes, it's not a problem. But there can be cases when they carry the same gene, although again, we're talking about relatively small numbers here. No value judgments in that, but we should understand the size of the compelling case there.

So now let's turn to common polygenic diseases? Well, the suggestion is that we could decrease disease risk and thereby enhance the human population. But I have to let you in on this secret. All those genes that have been linked to for common disease have exceedingly modest effects on risk. There are a handful that have effect sizes like three- or four- or five-fold. But 99-plus-plus percent have effect sizes less than a 1.2-fold increase.

Why do they tend to have weak effects? Well, the reason is that evolution beats down the frequency of alleles that have very strong effects. Evolution selects against them, and they become less frequent. In addition, it turns out disease processes are complicated and they are buffered. A missing gene will make a difference only when it occurs along with a number of other factors.

Let me put this in concrete terms by going back to C4. Schizophrenia risk in the population is 1%. If you happen to inherit the C4 allele associated with higher risk of schizophrenia, you now are facing a risk of 1.1%. That's it. It's a really important discovery from the point of view of uncovering a disease mechanism that is likely at work in many patients and may lead to real treatments over time, But, the risk conferred by the common genetic variants in this gene is not a risk you would even notice.

Now what if we were to take the top 108 genes that I told you about and create a polygenic risk score for each? We will note which allele is more risk-causing and which less risk-causing, We will weighted each locus by how much it contributes. If look at the top decile of the population for gene scores associated with the top 100 loci, these individuals have about a 3% risk of schizophrenia.

What if we include the top 10,000 loci in the human genome? That means we are willing to include many things that are not statistically significant (because we can't tell what is statistically significant). If we use a gene score based on the top 10,000 scores, the top decile of the population now has a 10% risk of schizophrenia. So if you were interested in 'fixing' 10,000 loci in the human genome, the risk for the top decile could be brought back down.

But is that a free lunch? Or will things happen when we mess with 100 or 1,000 or

10,000 loci in the genome?

Well, there is no free lunch, or at least rarely a free lunch. Genetic variants tend to have what we call pleiotropic effects. They affect many different things, and they also interact with environment. For example, we know that there are variants that lower risk of one thing but increase the risk of something else. For example, eliminating the CCR5 gene greatly lowers your risk of getting HIV, but it also increases your risk 13-fold for acquiring a fatal case of West Nile. We could edit the whole human population to eliminate the CCR5 gene and we will be protected against HIV, but now we will be much more at risk for fatal cases of West Nile.

There tends not to be free lunches, and in any case we have a pretty poor idea for most things about what their overall effects are. We have relatively little data. We discover that a variant has an effect on some disease. We don't have an index of all the other things it may be doing with respect to risk of other diseases, especially in combination with other genes in different environments.

So is it plausible to think about avoiding all the deleterious variants in the genome? No. Most have very small effects, and there is a small number with large effects. Should we go around and bestow upon everybody protective variants with large effects?

Well, there are a handful of cases of genetic variants that offer three- or fourfold protection against a disease, as with CCR5 and HIV. But to know that it would be safe, they'd have to be pretty common, so that we could observe them in the homozygous state. We don't want to give people a variant that turns out to be good in the one dose but bad when you inherit two doses. And, we'd ideally want them to have no downsides—no undesired pleiotropic effects, which isn't that easy to know at this point. With electronic medical records and fill genotypes on millions of people, we might be able to be able to get to the point that we could know, but today we simply don't know enough.

The best two candidates I can think of are ApoE and PCSK9.

ApoE2 and 3 look like they are much better to have than ApoE4, which increases your risk of Alzheimer's disease and some forms of heart disease. However, I can't swear that there isn't some problem here, because after all, ApoE4 has remaining around 3% allele frequency in essentially every human population. If ApoE4 had no benefits, nature should probably have gotten rid of it by now. But maybe not. Perhaps it is just at 3% frequency in all populations just by chance. Still we ought to keep our minds open. It's not to say we shouldn't do something about it, but we have to recognize the limits of our knowledge here.

Individuals who do not carry functional copies of PCSK9 have much lower LDL levels and much lower risk for heart attack. There are some homozygotes in the population, and the few that have been looked at seem pretty healthy. The most famous case is an aerobics instructor that is homozygous null for PCSK9. Still, we have quite incomplete knowledge. We have very few cases like this, and we have pretty incomplete knowledge on most of them.

What's the upshot? The decisions to be made about whether and where to use human germline editing involve many value judgments, but they have to be informed by the facts of the genetic architecture of disease.

With rare Mendelian diseases, the vast majority of situations can currently be addressed by in vitro fertilization and PGD. There are some compelling cases, although they are rare, and if we wish to avoid devastating genetic diseases, the best thing to do from a population point of view, from a public health point of view, from a caring about parents point of view, is to make

sure that parents have easy access to genetic testing so that they know that they are at risk and can use conventional PGD.

With common polygenic diseases, it is great to hear people talk about how we are going to give intelligence to the human population and athletic ability and all sorts of things like that, but the truth is these are very complex traits—often influenced by hundreds of genes. Height,for example, has at least 400 contributors, and together they explain only a small part of it. These are really important scientifically because they reveal the actual underlying biology and the processes and the point of therapy. But for the vast majority of individual variants, the risk is small, and even if you want to gang together and CRISPR-ize hundreds at a time, the effect will be relatively small.

Currently I can only think of a relative handful of things that would be plausible cases to try to do, and even then I don't know for sure that they are a good idea, because, again, if it is such a good idea, I want to scratch my head and ask why didn't evolution think of increasing its frequency in the population.

Bottom line: My prescription is humility. It is always good to remind ourselves, especially when we have in our hand an amazingly powerful tool like CRISPR gene editing, that we exist in a state of very limited knowledge, and human genetic disease is complex. We still have a lot to learn, and it might, might, might be a good idea that—before we make permanent changes to the human gene pool—we should exercise considerable caution.

ROBIN LOVELL-BADGE, THE FRANCIS CRICK INSTITUTE
APPLICATIONS OF GENE EDITING: GERMLINE MODIFICATION

The title of this session is "applications of gene editing technology in human germline modification." Before we start, I would like to stress that all the panel members of this session would be failing in our duty as scientists if we did not suggest what might be possible with the new genome editing techniques. These include some applications involving heritable germline alterations that might be achievable in the near future. Others would be a very way long way off if ever.

However, the mere fact we make these suggestions does not mean that we advocate that they should be done. We are just raising possibilities. Not only does our scientific knowledge fall short in many cases, but the decision as to whether to go ahead with any specific application or type of application is not one for scientists to make alone.

We are living in an age when humans have modified just about all aspects of our environment, deliberately or accidentally, whether it is climate, landscape, crops, animals, or many others. In this context it seems worth asking why would we not also want to modify ourselves? Indeed, one could argue that we have actually already been modifying our genomes, although in subtle ways and without necessarily thinking about it, through changes in our diet, public health measures, improving medical care.

A paper just published in *Nature* suggests that the version of the gene related to the allele responsible for lactase persistence, which allows many of north European descent to eat milk products as adults, became prevalent only around 4,000 years ago. This isn't so long ago in human evolution. I am sure that there are many other changes that have been induced by what we have done to what we eat and our environment.

Indeed, studies like this illustrate how much we are learning about the human genome and variation within the human genome, and this topic itself provides one of the backdrops to why we are having discussion about germline gene modification now. In fact, this topic, as has been alluded to, has come up many times over the past 40-plus years. Every time a relevant new method is introduced, whether it's transgenic mice, in vitro fertilizaion, human embryonic stem cells, cloning, et cetera, the topic has been debated.

In the past, however, it has always been very easy for scientists to simply dismiss the possible transfer of these technologies to modifying the human germline by saying, well, we don't know enough about genes, and besides, the techniques will not allow any alteration to a genome to be done in a way that is efficient and sufficiently safe.

However, we seem to be rapidly getting to a point where we can no longer deny the possibility, and that is evident from the talks we heard this morning and from talks we are going to hear later in the meeting as well.

I am going to just give again a little quick background to the session. Why this debate now? Well, the CRISPR/Cas9 system is simple, highly specific, highly efficient. You have the ability to multiplex, and it is versatile. It differs in essential ways from the previous technologies, which were all pretty much inefficient, not always very specific, definitely unsafe.

Also, there are many potential reasons for carrying out genome editing with human cells, including those from the germline, in early human embryos. These can be basic understanding of aspects of human biology, the role of specific genes and processes, to create

and study models of human genetic disease in vitro, to treat disease as somatic gene therapies, potentially to make germline therapies to avoid or prevent genetic disease, and finally one that seems to excite most people, the germline alterations to give some form of genetic enhancement.

I'm not going to talk much about the second and third of these points, which will be discussed in a lot more detail elsewhere in the meeting. But I want to just briefly outline some of these topics.

As far as in vitro, to provide understanding of human biology, there is a huge amount of work going on now using all these techniques to understand the role and mechanism of action of specific genes or gene pathways, understanding specific cell processes, such as cell-cell interactions, cell movement, cell lineages, and embryonic development, how these are specified, et cetera. We are exploring the use of stem cells in vitro to screen for molecules that can either influence these processes in a beneficial way or which are harmful, and we have heard brief mention of these types of approaches.

Such work already takes place with a variety of human cell culture systems in vitro—for example, organ-specific stem cells, such as neural stem cells and gut stem cells, which you can grow as simple cell culture systems or more complex three-dimensional cultures. Embryonic stem cells and induced pluripotent stem cells can be differentiated in vitro to not just individual cell types but a variety of complex tissues, such as cortical brain structures, optic cups, pituitaries, kidney-like structures, et cetera. So you can manipulate genes in these contexts to learn a lot about human biology.

Why not use the techniques to study also the early biology of preimplantation embryos and other germline cells? We are going to hear a lot more about this tomorrow from Janet Rossant, but just very briefly, there are different sorts of reasons why you might want to carry out research and apply that research, which doesn't necessarily require using these techniques for the application, but the research itself is really important. So it's to give better understanding of the biology of the early human embryos, including how cell types are specified in the early human embryo and of the genes involved.

Other topics include the ability to derive and study stem cell lines representing cell lineages thought to exist in the early human embryo, including progenitors of essentially the yolk sac, better understanding the role of specific genes in human germ cell development. We will hear something about this later in this session, including the differentiation of sperm and eggs, and actually just pure research on the genome editing techniques themselves.

Now you may think, why would you need to do that, unless you were planning to use them for some real germline application? Well, of course, the better your techniques are, the better the results you get from understanding early human biology, the fewer embryos you use. So there are many advantages of also researching the techniques in early human embryos.

There are a number of stages at which genome editing could be used to modify animals or the human germline. The earliest possible stage, if you are talking about the developing embryo, would be at fertilization, coincident, for example, with the injection of a sperm and the process called intracytoplasmic sperm injection, which is now a very common technique used in IVF clinics to guarantee you are going to produce a fertilized egg. You could simply mix the components together with the sperm and inject into the egg.

You could do this in zygotes, injecting the components into the cytoplasm of one-cell

fertilized eggs. When people have been doing work using these methods in animal models, particularly in mice, this turns out to be the incredibly efficient way of introducing your genetic alteration into mice. So if you are just making a simple mutation relying on non-homologous end joining process, it can be up to about 100 percent. So it is incredibly efficient.

To do more subtle changes is less efficient, but still far more efficient than we have had for any other previous methodology.

You could also introduce the techniques a bit later, with two-cell to blastocyst stage embryos. A blastocyst is a ball of about 100 or so cells, but in this case the genome editing technology is unlikely to work in all cells in the same way or all cells at all, which would give you mosaics, meaning that there is a different genetic constitution amongst different cells within the embryo. Perhaps we could overcome that problem using viral vectors in the early embryo, which is in theory possible.

In theory you could also use viral vectors to introduce the components to edit genes in post-implantation stage to deliberately infect germ cells in the embryonic gonads. I don't think anyone has done that or has attempted to do it, but in theory it would be possible.

Postnatally, you have maturing eggs in the ovary. I suspect that is going to be a rather very inefficient way of introducing any changes.

Finally, you could in theory, and there a lot of people working on trying to develop these methods, obtain gametes entirely in vitro from pluripotent stem cells, so eggs and sperm. This opens up many avenues for manipulating the genome, because you have an unlimited supply of eggs and an unlimited supply of cells that give rise to sperm, et cetera. So watch this space.

So why would you want to do germline modifications? Well, to avoid, prevent, or treat genetic disease. Correcting genetic defects in early embryos or via germline cells could hopefully provide beneficial consequences for the child born and subsequent generations. There are a number of situations where this may be of relevance: correcting infertility due to Y chromosome defects, correcting dominant mutations leading to congenital or late onset disease, correcting recessive mutations, including, for example, where loss of heterozygosity of a tumor suppressor gene in somatic cells is likely to lead to cancer, or perhaps altering an allele associated with disease risk to one that is protective.

Then there are a number of different categories that we can lump together under genetic enhancement. Maybe we could engineer the genome in such a way that the individual born would be resistant to an infectious disease or to cancer. We might be able to eliminate intolerance of certain foods such as lactose and gluten. Getting a little more adventurous, we might be able to add the ability to obtain nutritional benefits from plants or parts of plants that we can't currently eat and digest.

We could think about enhancement of various human traits—physical traits such as muscle mass or type, height, appearance, specific characteristics such as perfect pitch. Perhaps longevity. Scientists are beginning to understand more and more about things that affect how long we live. Maybe you could alter genes to allow us to live longer.

Finally, intelligence. Of course, we don't know enough to be able to do a lot of this stuff, and I'm not pretending that we do. Certainly for intelligence we are an awful long way off from understanding anything like enough about the genes involved in this to be able to enhance anyone with this technology.

These are all traits that may already preexist in humans, but you could also think about

enhancements which involve nonhuman traits, which range from the trivial—making people glow green, very useful for discos, but not much else—to altering sensory systems. There are animals that can see in the UV or infrared or detect electromagnetic fields. That might be cool. Tolerance to droughts, heat or cold. There are animals and plants that do all of these things.

Then of course there is the possibility of having completely synthetic genes and completely new traits.

JANET ROSSANT, THE HOSPITAL FOR SICK CHILDREN AND THE UNIVERSITY OF TORONTO
APPLICATIONS OF GENE EDITING TECHNOLOGY: BASIC RESEARCH

It is a very exciting time in genetic research with all the new tools of genome editing. My role here is not to talk particularly about the tools, although as a developmental biologist and a geneticist we are using the tools of gene editing every day in mice to study gene function and model human disease. It's changing the way we undertake research.

I have been asked to talk a little bit about why you might want to apply the tools of gene editing to a human embryo not for germline manipulation, but really to help understand more about the human embryo itself

Why is it important to understand how an early human embryo develops? To gain insight into the fundamental question of our own origins. Where do we come from? How do we get from the fertilized egg to an organism?

But there are practical implications of understanding how the early human embryo develops because it is those stages that are used for in vitro fertilization (IVF) and other reproductive technologies. By understanding them, we can begin to understand how to improve success of IVF and prevent early pregnancy losses. Importantly in the stem cell era, it is from the early embryo that pluripotent cells arise; understanding human development will give us insight into the origins of pluripotency, the origins of the placenta, and how to translate that knowledge into improved stem cells for regenerative medicine.

We have learned a lot from studying the mouse embryo, and we can predict that there will be fundamental similarities between mouse and human development. so we are not starting from a blank slate. However, the more we investigate the human the more we can expect to find differences as well as similarities.

In the mouse and the human, the first stage when different cell types develop in the embryo is the blastocyst stage. The blastocyst has about 100 cells, is the size of a speck of dust and contains only three cell types. There is an outer layer of trophectoderm, which gives rise to the trophoblast layers of the placenta. The inner cell mass has two cell types: primitive endoderm, which gives rise to yolk sac endoderm, another extra-embryonic membrane, and the epiblast cells.

The mouse and the human and all mammalian embryos spend their first few days of life making mostly the cell types that they need to survive in the uterus, the placenta and the yolk sac. The epiblast cells that are set aside are the pluripotent cells that give rise to the entire mouse including its germ cells.

What we also know is that by the time you see that blastocyst, the three cell types are really restricted progenitors to those later lineages, and you can capture that progenitor state in stem cells. There are three kinds of stem cells you can obtain from a mouse blastocyst, the most famous of which are embryonic stem cells. They are the cells derived from those pluripotent epiblast cells, and they retain that pluripotent capacity for endless generations in the petri dish, expressing pluripotency factors and dividing indefinitely.

But if you put them back into a blastocyst, they contribute to the entire fetus, including its germline, but they don't make the yolk sac or the placenta. The other two lineages, trophectoderm and primitive endoderm give rise to trophoblast stem cells and XEN progenitors, which also grow indefinitely in culture. When you put those cells back into a

blastocyst, they contribute to the placenta and the yolk sac, respectively. So we have a very nice experimental system in the mouse in which permanent cell lines from all three blastocyst lineages can be used to study this process of lineage restriction.

But if we think about how you get to a blastocyst, that is the fascinating part. How do you go from an egg to an organism—that's what we all want to know. But what about just the first decisions? How do you go from an egg to a blastocyst? You start with a single cell that divides over the first few days of development to, in the mouse, about 64 cells where you begin to form the blastocyst with the inner cell mass, and then the inner cell mass makes the epiblast and the primitive endoderm.

What seems to happen in the mouse is that this is a gradual process where cells start as totipotent—a single cell can form anything—and then gradually they become restricted so that we get pluripotent and trophoblast cells.

When do they lose this capacity? What is the process, and what are the molecular mechanisms behind it? Well, in the mouse, we can do a lot of experiments, in which we dissociate embryos at different stages and ask whether they can change cell fate to address these questions and begin to get some insights. A number of experiments suggest that restriction is progressive but complete by the blastocyst stage, with expression of a key gene, *Cdx2*, marking the outside cells that will become restricted to trophectoderm. Inner cells will turn off *Cdx2,* express pluripotency markers like Oct4 and become pluripotent. So what about the human?

There have been some experiments on the timing of lineage restriction performed on human embryos, not with as much precision because of the restricted number of embryos available that have been consented for research from IVF programs. The data to date in the human suggest that lineage restriction occurs later than the mouse, probably not until after the blastocyst forms. Why is that? Does it relate perhaps to the timing of the expression of these lineage specifiers that we start to see being expressed early in the mouse? Indeed, it probably does.

Kathy Niakan and Kevin Eggan have studied Cdx2 and Oct4 expression in different stages of human development. They found that Cdx2 does not begin expression until after the blastocyst forms. And Oct4 is expressed broadly and overlaps with Cdx2. Their expression patterns do not separate until really quite late in blastocyst development, unlike the mouse. This means that there is likely a difference in timing of lineage specification if nothing else. Does that mean we have a upstream different mechanism?

In the mouse the mechanism that restricts Cdx2 to the outside cells turns out to be a special signaling pathway called Hippo signaling. Hippo signaling activated in the inside cells actually blocks Cdx2 expression and prevents those inside cells from forming the trophectoderm. Disruption of any essential component of the Hippo signaling cascade during these early stages turns all cells in the embryo into outer trophectoderm cells and no pluripotent inside cells are formed So this signal determines whether the embryo can actually make a functional inner cell mass or trophectoderm.

Well, is Hippo signaling important in the human? We don't know. Possibly not, because it is activated by differences between inside and outside cells that occur prior to blastocyst formation and yet, in the human Cdx2 expression does not even begin until well after formation of the blastocyst.

So what about the next decision? The blastocyst has made an inner cell mass and now has to set aside the pluripotent cells, the epiblast, and make the primitive endoderm. We know quite a lot about that in the mouse, too. We know that the inner cell mass begins as a mosaic of cells expressing primitive endoderm genes like Gata6 or pluripotency genes like *Nanog*. Over time, these two lineages sort themselves out to segregate the epiblast and primitive endoderm layers one day later.

We also know that the initial difference between epiblast and primitive endoderm lineages is set by the level of activity of another signaling pathway, the FGF signaling pathway. FGF signaling, is required to make primitive endoderm. If you block FGF signaling, all the inner cell mass cells become epiblast. If you activate FGF, all the cells go the other way and become primitive endoderm. So we believe that cells are reading out local signal strength to decide whether to become epiblast or primitive endoderm. This is a really interesting process and not well understood.

What about humans? Again, there isn't a lot of information, but experiments to date suggests that FGF signaling may not be the key player in this lineage decision in the human embryo. If you take human embryos and treat them with FGF or ERK inhibitors, which we showed turned all inner cell mass cells to epiblast in the mouse, it does not seem to affect lineage decisions at all. Resulting blastocysts make epiblast and primitive endoderm quite happily. So is there another mechanism for lineage segregation in humans?.

Understanding the role of FGF signaling in the mouse embryo has been critical to deriving the three stem cell lines from the blastocyst because those cells are derived them in FGF conditions that reflect how the cells respond in the blastocyst itself. ES cells, particularly what are called naïve ES cells, are isolated in conditions that block FGF signaling, so you prevent primitive endoderm formatin and maintain beautiful pluripotent embryonic stem cells.

If you activate FGF in the embryo it pushes cells towards primitive endoderm: that is how we can isolate XEN cells from inner cell masses of blastocysts. What I didn't tell you is that FGF is also required in the blastocyst to make the trophectoderm proliferate. If you grow trophectoderm in the presence of FGF in the petri dish, you can isolate trophoblast stem cells. So different FGF conditions determine the stem cells you can obtain from the mouse embryo.

Is this the same in the human? No, different, again. Human embryonic stem cells, when they were first derived by Jamie Thompson, were derived in the presence of FGF, which would have promoted XEN cells in the mouse. Active FGF signaling is required to maintain human embryonic stem cells, which we now think may be in a really different developmental state from mouse embryonic stem cells.

There have been a number of attempts to generate naïve human ES cells that are more like mouse ES cells. , It is not enough just to block FGF signaling; multiple different complex culture conditions have been reported to generate cells that more closely resemble the mouse naïve ES cells. And you can't make human TS cells from human blastocysts. The human trophectoderm does not seem to respond to FGF in the same way as in the mouse.

So we still have a lot more to learn about the human embryo, the human pre-implantation stages, including the molecular pathways and timing of restriction and how they relate to stem cell derivation. We're beginning to get some more insights as the tools to be able to study small amounts of tissue and even single cells come into play. Single-cell RNA-seq, a method to look at genome-wide gene expression, is being applied to early human embryos. A

number of different studies that have been published and there are more to come. What we know so far—and there are still differences and similarities between the studies—is that, indeed, there are similarities with the mouse but that there are differences in the developmental profiles of gene expression and some of key players between human and mouse pre-implantation development.

The early post-implantation stages of mouse and human development also differ morphologically and perhaps in other ways that we don't understand at all. After implantation in the uterus in the mouse, the epiblast forms a cup-like structure, the egg cylinder; the human epiblast spreads out and forms a germ disc, so the morphology is very different. The early trophoblast proliferates in the mouse but is highly invasive in the human. Big differences that we have to understand but cannot because early human post-implantation development is of course inaccessible to experimental study.

So there are many questions about human early development. Is Hippo important? What is the role of FGF signaling? Does TGF/Nodal signaling, as has been suggested, play a stronger role in human than in mouse? Why can't we derive human TS cells? Is there actually a naïve pluripotent state in human development at all? And to address early post-implantation development differences, can we develop culture conditions to study early post-implantation development from blastocyst up to germ layer formation in culture, the 14-day deadline imposed by regulatory restrictions?

To do that, we need to develop carefully controlled methods for efficiently studying human development, under approved ethical guidelines. Better culture systems for early and later development combined with better ways of functionally analyzing human lineage restriction will lead to better understanding of the fundamental processes of human development.

CRISPR/Cas9 gene editing has a key place in the tool set you would want to use to understand human development. CRISPR/Cas9 guided activation or inactivation of epigenetic modifiers could be used to understand overall gene regulation in development. Indeed, if efficiencies of CRISPR/Cas9 continue to be increased, it should be possible to make mutations to directly study the function of candidate genes for regulating cell fate in the early human embryo.

All of these experiments would not be, in any way, experiments that would involve germline modification. These would all be *in vitro* experiments carried out at the blastocyst or early outgrowth stage.

There are many reasons to continue trying to understand human development, of course under very careful guidelines. Any work with human embryos itself obviously has ethical and regulatory constraints, but none of these experiments necessarily lead inevitably to germline modification.

SHARON F. TERRY, GENETIC ALLIANCE
SOCIETAL IMPLICATIONS: THE ROLE OF ADVOCACY ORGANIZATIONS

I am going to talk about advocacy organizations and emerging technologies. I am here because I have two children who have a genetic condition, an autosomal recessive condition. They were diagnosed in 1994, and in 2015 I would say they are happy and healthy people who live with a genetic condition that will cause vision loss, gastrointestinal disease, and cardiovascular disease. My passion for this is purely as a parent, and it drove us, my husband and I, to found a foundation that has attracted the involvement of many advocacy organizations and that functions not only as a recipient of technologies and research, but also a purveyor of those things.

We are engaged in managing essentially all the research in the world on this rare disease. That is not uncommon these days. It was uncommon 20 years ago when we built a biobank and created a genetic test and did some of the other things that we thought were important to getting to a solution.

So I want to make it clear that I am a passionate parent who wants to find solutions for disease or the ability to live with disease and conditions in the world. I am also interested in this on a systemic level. So we build systems we hope are enduring, that will be more integrated into the research paradigm, all the way out into the services and clinical realm.

I'm also the CEO now for the past 12 years of the Genetic Alliance, which is an coalition of advocacy organizations and others, thousands and thousands of organizations. Twelve hundred of these are advocacy groups that are dedicated to genetic diseases, and we are working to accelerate development and access to interventions but always through the patient/participant/consumer perspective. So we start there. Our language is there. Our way of working in the world is there.

Advocacy organizations are as heterogeneous as the diseases that they represent—everything from kitchen table groups to mini-pharmas. They deal with ultra-rare to common conditions, different levels of heritability, all across the lifespan. We have variable morbidity. Some diseases are lethal, some are not. Some diseases are difficult to live with; some are not so difficult.

There are groups that focus on the support realm, the research realm, and everything in between—but certainly moving more and more toward the research realm in recent years. There are top-down groups where one leader makes all the decisions for the group, and grassroots groups in which decisions are made democratically or there is no single group position. So when I talk about advocacy organizations, I can't really talk about one thing. I certainly can't represent those organizations, but I can give you some of the flavor of how they think.

I conducted an informal poll over the past few days to ask people from these groups what they think about gene editing. The first person wrote back “Hell, yes.” The next one said the only way we will make any progress in getting better outcomes in our community is with gene editing. Others said we need to fully explore this; we need to look at this scientifically; we need to look at the ethics. Somebody said “Gene what?” Another group reported that it is already engaged in research on gene editing.

So to edit or not. I think one of the questions we must confront is when is a condition a

disease or a problem. From my little survey I hear comments like: “Well, we don't want you to start editing intersex conditions.” “We don't want deafness edited away.” We don't want Klinefelter's or Turner syndrome or maybe Down syndrome, and other things. What about achondroplasia, dwarfism? That shouldn't be considered a condition, or should it?

The community is having these conversations. They have already started them because preimplantation genetic diagnosis is already being used by people to avoid having children with spinal muscular atrophy or Down syndrome. People then ask “What about my child with that condition?” Does that child have a community of similar people? Are we actually de-diversifying the population in a way that we haven't considered?

I think from the advocacy groups’ point of view we are looking at a world in a very different way, because we come from communities that live with various physical conditions, and as my children are often telling me--and they are adults now—stop fighting disease and live with disease. It's part of what is normal.

So all of which is to say I still work every day working toward interventions. So I think the bottom line for us is that we need a type of tempered urgency, and we are beginning to talk about this hear, and I think we need to continue to talk about it. I think the needs are enormous and immediate. We heard that in the last panel, a lot about how do parents drive this? How do consumers drive this?

It's not because we want to have some fun. It's because we want to figure out how do we alleviate suffering, and that is a worthy goal, and we need to figure out is this one of the ways that that would be done and how would it be done. I think those are really clear and important questions.

The technical and ethical issues must be resolved satisfactorily, and I probably could have even used a stronger word there. I am being slightly careful, because I'm on the committee. So I am not giving you my opinion until we do our deliberation for almost a year. But we really want to have this dialogue in a way that is meaningful and that we get to the resolution that we are starting to see, but I think we need to go a long way more.

We need accessible technologies. I think one of the exciting things at least in the advocacy group conversations is CRISPR/Cas9 is exciting because it seems more accessible than some of the technologies that we have heard about before that might be more difficult to actually do clinical trials with.

So again, my peers, the moms and dads who have kids now who are working in this realm are looking for ways to do more research more quickly to impact things, whether it is in vitro or in vivo.

Data sharing and transparency to accelerate the process. One thing I would just wonder is what if we said part of this social contract for deciding whether or not this technology is safe and we are ready is if we said let's share everything we learn in this space with each other, and that is a theme for me overall, but I think it would be very interesting to be applied to gene editing and to see whether or not we would learn more quickly if we didn't compete with one another and if we didn't worry about patents and commercialization immediately, et cetera, and instead looked at other things, other ways of doing things, perhaps like the semiconductor industry did.

And the last thing here I will say is the regulatory dialogue has to be concurrent with technology development, and I know we are going to talk again more about that tomorrow, but

I think we need to think about how do we regulate -- I think Alta's tee up in the beginning of the day was a good one -- in such a way that we are more flexible, we are more realistic about how we need to move? FDA has struggled a long time with even just genetic testing. What kind of FDA do we need to be considering gene editing? How do we need to consider that technology in a way that does leave that dialogue open to an evolving regulatory system?

And the very last thing I will say is I think what we are looking for is hope and not hype, and it is very easy to cross the line into hype. We have seen it done over and over, and I am hoping we can have this dialogue in a way that includes the very people who will use it, which is all of us, but also keeps it in a really robust way in terms of what is evidence development, how do we manage that evidence development, and how do we pace ourselves in such a way that it is responsible?

BARBARA J. EVANS, UNIVERSITY OF HOUSTON LAW CENTER
GOVERNANCE AT THE INSTITUTIONAL AND NATIONAL LEVEL

Are existing laws adequate to regulate human gene editing? The fact of the matter is that they may have to be adequate, because the technology is here, now. You have to "go to war" with the regulations you have, not the regulations you wish you had. That may imply a need for careful legal analysis and close dialogue with regulators, to get the most mileage out of the regulations we have.

I actually like the U.S. Food and Drug Administration's (FDA's) framework of research regulations for oversight of gene editing—and I fully appreciate the irony of that statement. Those of you who know me know that I've spent much of my law practice trying to keep FDA off researchers' backs, but FDA's research regulations offer some excellent tools for managing the risks of human gene editing.

Many people have at least some familiarity with FDA's premarket approval processes for medical products such as drugs, biologics, and devices, but may be less familiar with FDA's research regulatory framework. FDA's research regulations include a basic set of ethics rules that require informed consent, conflict disclosures, and review by an ethics body—an Institutional Review Board or IRB. I think we all have doubts about whether a simple ethics framework that requires informed consent and ethics review is sufficient for regulating gene editing. I agree very much with Alta Charo's remark on Day 1 of the Summit that we need to regulate not just the technology, but also regulate the specific products. I would go further and add that we also need to regulate the specific uses of the products, because we're all concerned about off-label use. Fortunately, FDA has additional research regulations that actually let you do those things. These include FDA's Investigational Device Exemption (IDE), Investigational New Drug (IND), and Investigational New Animal Drug (INAD) regulations. These regulations make it lawful to sell or ship an unapproved (experimental) product only if it will be used in an FDA-approved research protocol. Any other use would be unlawful. That allows FDA to place very tight controls on how a gene editing product can be used.

There's a misconception that FDA regulates only commercial research that aims to bring new products onto the market. That's not true. FDA also can regulate non-commercial, academic research in various circumstances. For example, FDA guidance in 2013 makes it clear that academic researchers need to obtain an IND for drug research—even if the research uses an already-approved drug—if the research explores an unapproved "route of administration, dose, patient population, or other factor that significantly increases the risk (or decreases the acceptability of the risk) associated with the use of the drug product." In other words, FDA can regulate off-label uses of an approved drug in research if the use would place research subjects at incremental risk as compared to the already-approved use. The IDE regulation for device research is even more explicit. It defines a device as having "significant risk" if it "presents a potential for serious risk to the health, safety, or welfare of a subject." FDA can require an IDE for significant-risk research even in academic settings where there is no intent to commercialize the device. That was displayed recently when FDA asserted jurisdiction over a group of newborn sequencing studies that were traditional, publicly funded academic research carried out at universities.

Another important point is that FDA's research regulations have meaningful enforcement provisions. Violators do not just get a slap on the wrist the way we sometimes see when ethics codes are violated. FDA can impose meaningful civil and criminal sanctions for violations of its IDE, IND, and INAD regulations.

An important question in applying FDA's regulations is whether gene editing technologies should be regulated as drugs or devices. The regulatory definitions of "drug" and "device" share several common elements. From a purely legal standpoint, many technologies could be characterized as either a drug or a device. In a 2011 guidance, FDA stated that when a product meets both definitions, FDA "generally intends to classify the product as a device" although FDA has the final say and would weigh many factors when making that determination.

The main distinction is that a device does not achieve its primary intended purpose through chemical action or by being metabolized. We traditionally think of devices as working through mechanical or electrical principles. At the microscopic level of CRISPR-Cas9 and similar technologies, this distinction may not be meaningful. FDA's definitions seemingly would allow the agency to characterize CRISPR-Cas9 as either a drug or a device. The distinction may be important, because there are potential advantages in framing it as a device—in effect, conceiving CRISPR-Cas9 as a little pair of scissors and little genetic prosthetic that is inserted in a person's genome.

The advantage of framing it a device is that FDA's drug and device regulations define human subjects differently. Somatic gene editing is currently regulated under FDA's IND—or drug—regulations. That seems appropriate because somatic editing involves putting a chemical into a living person, analogous to administering a drug.

The difficulty with germline editing is that it manipulates embryos and gametes, which probably do not meet the definition of a human subject in FDA's drug regulations. The IND regulations seemingly would not apply. In contrast, FDA's IDE—device—regulations have a wonderful clause that a human subject includes a person on whose specimen an experimental device is used. A person who donates a gamete that is manipulated is a human subject, and that invokes the IDE framework and gets it active, allowing FDA to regulate the research.

There are other good features of FDA's device framework. For example, it is designed to accommodate niche technologies. Many devices serve very small markets. FDA's drug regulations treat a product as an "orphan drug" if it serves fewer than 200,000 patients per year, which is a much larger market than many medical devices ever attain. FDA understands that it would not be economically feasible for device manufacturers to conduct large and costly clinical trials—like the ones FDA requires for almost all new drugs—to prove the effectiveness of a device that will only serve a few patients.

The device regulations adjust FDA's premarket evidence requirements for devices that serve small markets. There is a humanitarian device exemption for devices that serve fewer than 4,000 patients per year and a custom device category for devices, like orthodontic appliances, that sell fewer than five copies per year. A gene editing product for a very rare genetic disease might well qualify as a custom device and be able to benefit from a less-onerous premarket review process.

One option for regulating gene editing products would be keep them as experimental devices—in other words, keep them subject to FDA's IDE requirements—so that the use protocols are perpetually subject to FDA oversight. The problem with that approach is that

insurers are reluctant to reimburse products that remain experimental. So, at some point, people will wish to have these treatments cleared or approved for wider commercial sale. Then there is a wonderful feature called restricted device authority that allows FDA to grant a premarket approval for a device, subject to meaningful regulatory restrictions on its use, sale, and distribution. With some of the laser devices used in LASIK eye surgery, they even restrict what doctors can say about it to patients. So FDA's device regulations offer a way to place meaningful restrictions on what can be done with gene editing products after approval. Note, though, that if FDA ultimately prefers to regulate all gene editing products as drugs, it can impose similar use restrictions on drugs under the Risk Evaluation and Mitigation Strategy (REMS) provisions Congress enacted in 2007. FDA already has tools to manage high-risk off-label uses, and that is true whether gene editing is regulated as a drug or a device.

My second point is that legal policy analysis needs to be a lot more granular than previous law-and-genetics work has ever been. Law is a bit like genetics in that nuances matter: we don't talk about disease by talking about genes; we have to talk about specific gene variants. To address the issues we now are facing, policy analysis must evaluate nations' legal frameworks very carefully, and that means provision by provision.

We know that with gene editing we're not dealing with risk, where the probability of various outcomes can be quantified. We're dealing with true uncertainty, where we cannot even quantify the probabilities of extreme outcomes.

Consider this example: Studies of the dog genome suggest that variations in just a couple of genes may account for the size difference between a Chihuahua and a Mastiff. What if a couple comes to a doctor and says, "We want a designer baby. We want germline gene editing, but what is the chance that an unexpected, off-target effect may cause us to have a nine-foot tall daughter?" No doubt they would love the child, but the cost of clothing would be astronomical. It was a relief to learn, on Day 1 of the Summit, that hundreds of genes are involved in human height, so perhaps the risk is vanishingly small. The point of the example is this: We have some of the best minds in this field in the room, and I bet there is no one here who would be willing to place a numerical probability on how likely it is that an extreme event like that could occur. There is simply no basis to state a number, because we do not know the shape of the probability curves at this point, nor can we ever know them.

A 2000 OECD report noted that when confronting this degree of uncertainty, many nations believe it is appropriate to take a precautionary approach, but nations do not necessarily agree what "precaution" means. There are many different ways to implement a precautionary approach, and some legal provisions are more precautionary than others.

The most stringent approach is to impose a moratorium, to ban a technology altogether, which amounts to a presumption that its risks are very grave. I think we need to understand that the problems we are facing are not novel. There are other areas where good decision scientists are facing questions such as: What if we melt the polar ice caps? What if a nuclear waste dump springs a leak? What if we collapse the financial system? There has been a lot of thought about how to analyze serious, intergenerational risks in other contexts. We need to draw on that work. We need to get out of our medical bioethics "silo" and learn lessons from those similar efforts.

One lesson is that when considering a moratorium, policy-makers may wish to limit it to situations that threaten irreversible or catastrophic risks—a so-called catastrophic

precautionary principle. Also, it is unwise to ban the basic research that could resolve the uncertainty that is causing people to want to have a moratorium now. Evidence-forcing solutions offer a possible alternative: adopt policies that force the creation of evidence. As Alta Charo noted on Day 1 of the Summit, it can be very important where policy-makers place the burden of proof: Should they make the person who wants to do something prove it is safe, or should they make the government prove it is unsafe?

Another important line of work stresses the need for policy-makers to give weight not just to risks, but also to the benefits that could be lost if work does not go forward. It is a mistake to base policy on worst-case bioethics. We also need to look at the potential for public health benefits and recognize that banning gene editing technology may consign many people to very harsh circumstances. Research needs to progress cautiously, in pursuit of those benefits.

The problem with all this is I'm not sure we can agree what a catastrophe looks like in gene editing. I urge policy makers to be very precise about the specific outcomes they are trying to prevent. I do not buy into the notion that it would be a catastrophe if an undesirable off-target effect passes to the next generation, because if that is the definition, then unedited pathogenic variants are a catastrophe happening now.

I also lean toward the notion that a catastrophe would be something that has global impacts, or very broad effects, rather than impacts solely on the individual research subject. That is not to deny that individual research injuries can be devastating. Yet if individual injuries are viewed as catastrophes, then we must admit that many patients suffer catastrophes now in standard care.

I personally believe we are more likely to suffer globally catastrophic events from editing corn genomes and editing microbial genomes, than from editing the human genome. Corn is extremely promiscuous, and if you put a bad variant in corn, it will spread very far and could potentially damage a major food crop which would have worldwide impact. Humans, in contrast, are not that promiscuous. There have been a few characters in history, usually conquerors like Genghis Khan, who managed to insinuate their DNA into large parts of the modern population, but most of us do not reproduce so assiduously.

Another advantage, from the standpoint of managing risk, is that human research subjects are smarter than corn. If a research accident inserts a bad, off-target genetic change into a human being, researchers can reason with the person in a way they just cannot reason with corn. People who are research subjects are already altruistic. The researchers could say, "We're really sorry. We gave you a really bad off-target effect. Would you work with us to try not to spread it around?" And I think these altruistic research subjects would share the researchers' goal of minimizing impacts on future generations.

It is inaccurate to characterize some nations as having "precautionary" policies while other nations are "permissive." In reality, most nations have a complex mix of regulatory provisions—some precautionary and some not so precautionary—that aims to strike a balance that protects consumers while fostering innovation. Sometimes, there are wide variations in regulatory strategies even within a single country. Taking the U.S. as an example, the slides show that the regulations are more precautionary with some technologies than with others. Even within single categories—for example, drugs or medical devices—specific regulatory provisions may adopt a more precautionary stance at certain stages of the product life cycle or

in response to the specific product's perceived level of risk, and there are mechanisms that weigh both the risks and prospective benefits. Having a mix of regulatory provisions is how nations nuance their innovation policies. Different nations may choose to do it differently.

My final point is it is wise to be skeptical of widely held assumptions. As an example, discussions of how to regulate gene editing often start from an assumption that international harmonization is desirable. All assumptions deserve scrutiny.

There is no question that harmonization is good for business. Transnational corporations love it; this may be the only point on which bioethicists and transnational corporations agree. Harmonization also is good if the task is to manage really serious global externalities that could end civilization. When that is true, inconsistent regulation subjects all nations to the risks that slip through the most porous regulatory framework.

But if we're not dealing with potentially catastrophic risks, it can be good to allow national diversity, because nations have different cultures and different values. If we have different nations doing different things, we can run things in parallel and discover what works, and we can learn from each other. So let's not be too quick to harmonize.

CHARIS THOMPSON, UNIVERSITY OF CALIFORNIA, BERKELEY
GOVERNANCE, REGULATION, AND CONTROL: PUBLIC PARTICIPATION

I'm going to start by looking back on some of the things that we've talked about and seen between the beginning of this summit and now. This is just my take: I'm sure I've got all kinds of things wrong - maybe there's a lesson in that about the limits of communication - but I'm trying to summarize some of the positions that have been expressed.

Are we moving toward a consensus on human germline editing or not in this meeting? We've heard a lot of different positions (see box below).

"Yes" to human germline genome editing, in order from the most to the least permissive:

1. Edit the human germline genome for reproduction if it is no more risky than "natural" sexual reproduction and is aimed at eliminating serious genetic conditions.
2. Edit the human germline genome for reproduction if it is likely to be safe, effective and make a big difference. (For example, for monogenic/oligogenic serious medical conditions.)
3. Edit the human germline genome for reproduction to avoid having offspring born with a serious condition only if there are no other alternatives, such as in vitro fertilization with pre-implantation diagnosis. (For example, if both genetic parents are homozygous for the same serious medical condition so that none of their embryos would otherwise be free of the condition.)
4. Move toward editing the human germline genome for cultural and religious reasons, such as when a given national culture is pronatalist, has a pro-medicine ethos, and has significant state subsidies for reproductive and screening technologies.

"No" to human germline genome editing, in order from the most to the least permissive:

1. Hold off (place a moratorium) on editing the human germline genome for reproduction while we work out the technical issues of safety, off-target effects, efficacy, efficiency of the edit, and the development of a clinical grade delivery mechanism for the editing system.
2. Hold off (place a moratorium) on editing the human germline genome for reproduction at least until we (re)frame and make much more inclusive vital ethical, social, and economic debates around ableism and disability justice, the over medicalization of human variability, racism and sexism in science, local and global health inequality, the views of non-stakeholders as well as stakeholders, and the needs of future generations, the vulnerable, and other species.
3. Ban the editing of the human germline genome for reproduction because it is a reasonable line to draw against hubris and in favor of our human future, against a highly likely slide toward eugenics and the exacerbation of inequality, and against possible ecological and other harms.
4. Ban the editing of the human germline genome because of the moral status of the embryo, human dignity, the freedom rights of the genome-edited child, and/ or religious conviction.

The most permissive (of the 'yes' to human germline genome editing positions) we heard is to edit the human germline genome if it's no more risky than natural sexual reproduction and if you want to get rid of disease.

Second, do it if it's likely to be safe and effective and make a big difference, for example, for serious monogenic and oligogenic conditions.

Moving down the scale, edit the human germline only if there are no other alternatives such as PGD to avoid a serious condition, e.g., both genetic parents are homozygous for the same serious condition. This is essentially the approach advocated by Eric Lander.

Fourth, editing the human germline genome may happen – this was for the Israeli case – in that particular country because it fits a pro-natalist, genetic-screening-friendly, and pro medicine ethos that is subsidized by the nation in question.

These are very different positions but they all basically say that at least under some conditions it would be okay to edit the human germline genome.

Among the 'no' (to editing human germline genomes) positions, the first moratorium position was to hold off on editing the human germline genome for implantation while we work out the technical issues of safety, efficacy, delivery, and so on.

On the less technical and more social side, we heard pro-moratorium positions that recommend holding off on editing the human germline genome, at least for implantation purposes, until we reframe vital debates and learn to listen to and incorporate ideas of other stakeholders—and I would argue, non-stakeholders—future generations, the vulnerable, other species, and so on.

Then we heard a couple of positions that sound more like banning the editing of the human germline genome (rather than imposing a moratorium) because it is a reasonable or important line to draw. I heard a lot of concern that I share about becoming a selecting society.

The first of these positions is that prohibiting human germline genome editing is a reasonable line to draw against hubris, against eugenics, and against possible ecological and other harms.

The most restrictive position we heard at this meeting would be to ban editing of human germline genome because it's against the moral status of the embryo or some universal principle of human dignity.

I'm not going to try to decide among these positions here. I think everybody in the room is good willed on this topic, so I'm going to move on to some things that have also come up to do with possible misunderstandings and then bring it around to what we might do about the fact that there is such a variety of opinions.

1. First, the metaphors. There's been a lot of discussion in the corridors, on Twitter, and so on about the metaphors used in this conference. And I think this is very important for the public. We seem to have settled on 'editing' for this summit, and I can't work out why we sometimes say gene and why we sometimes say genome, but I hear both from scientists. We sometimes hear genetic modification, sometimes GMOs, usually in the context of crops. Recombinant DNA, gene surgery, gene therapy, all of these words, all of these expressions are used. What's the difference among them? What are the stakes?

What I would urge is that we don't pick one over the other just to avoid associations with that term. That carries the risk of the adult stem cell phenomenon (think Planned

Parenthood) where people were astonished to find out that fetal cells were considered to be adult cells in the context of adult stem cell research, where 'adult' means 'somatic' cells; everyday people, including most social scientists, see 'adult' as being a life course stage.

2. A second critical point is to understand and agree **which kinds of genome editing are germline** (rather than somatic). If embryos are edited but not implanted, it's not germline editing. Is that right? *If so, that would mean that someone opposed to germline editing could still accept editing of human embryos that are not implanted.*

Also, presumably, if gametes or gamete precursor cells are edited and then at any time later used for reproduction, *it is germline gene editing even though there wasn't any editing of any embryos involved*. This may be completely obvious to all the scientists in the audience, but I think it's really helpful to explain to the rest of us.

If pluripotent stem cells were derived, edited, and then used for reproduction, presumably then it would also be germline editing. So being clear on the subtleties of somatic versus germline genome editing would be very helpful.

3. Some of the things that I'm about to talk about have come up today, but I wanted to talk next from a social science point of view about some of the **missing debates and constituencies** at this meeting. I want to start by saying that the organizers worked incredibly hard to a very impressive effect to attend to a lot of these issues, but what ends up happening often reflects underlying social problems, not a lack of desire or will.

Disability. As Ruha Benjamin talked about this morning, disability perspectives were largely missing until that point. To be fair, Gregor Wolbring and Tom Shakespeare were invited but were unable to attend; luckily their perspectives were recently published in *Nature*. I'll just echo the disability justice position that "nothing about us is without us" is a great place to start for all conversations about deselection, cures, and the medical model of disability.

Race. Critical race perspectives again came up this morning with Catherine Bliss's presentation. Scholars have shown that modern science has been implicated with race and racialization from science's inception to the present day, and at the moment in the United States, for example, any question about how to govern a threshold technology that will affect us all should not be able to proceed without indigenous voices, African American voices, Latino voices, and migrant voices—especially this year.

Gender. At this summit, you'd be forgiven for thinking at times that men are from Mars and women are from Venus despite the amazing women scientists at the heart of genome editing advances and all the excellent speakers we've had. I hate the expression that men are from Mars and women are from Venus. All genders want to go to Pluto obviously. But we really just need to get this done. We need to pay attention and make sure we don't, for example, have panels on embryos and fertility as we had yesterday—even though every speaker was wonderful—that have no women on them.

Queer bioethics is a thriving field that is another site for how to think about things that were considered at one time or another to be medical disorders that needed correcting, needed to be subject to eugenic deselection, that we currently don't think of as medical conditions at all. Also, it's a wonderful site to think about the use of medicine in creative ways. Presumably somatic gene editing could be used in ways for self-expression, for non-normative purposes, and in ways that are outside of the 'pro-cures' biomedical frame.

Health disparities. What kind of health care system a country has and who has access to the fruits of what research should frame all debates in this area, as it should in all areas of health policy.

Commercialization. It's really important that we do translational science, that we get things to the market, that there's uptake of innovation. But what impact do intellectual property disputes and the investment landscape have on the field and on our views of what's acceptable?

Cross-border care and medical tourism. We know from our work on reproductive technologies and stem cell therapies that new repro-genetic technologies with pricing and ethical regulatory differentials from one country to another set up all kinds of sending and receiving pressures that can become problems in and of themselves.

Bioart and biohacking. What are the creative and democratic potentials of these techniques? I'd like to think for all kinds of reasons to do with gender and other things that it's not just two boys in a garage, but that there are all kinds of spaces where we can do creative work that's artistic and disruptive.

Biosecurity. Are the very real national security biosecurity risks of genome editing exaggerated for citizen use of these technologies? Are citizen inventions benign because they're just headed to high street commercialization of these technologies? Will it be like hair salons for each bit of somatic gene editing? Or will citizen uses of human genome editing be something more impressive and more important to the cultural archive of our nations?

Other species. What can we learn from genome editing that happens naturally within and between other species including between ourselves and our microbiomes? The rest of us don't know enough about this. It would be really helpful to keep reminding us about what happens normally. What kinds of mutations? How much exchange between genomes happens 'naturally'? Should this make us worry less about germline editing in humans?

RUHA BENJAMIN, PRINCETON UNIVERSITY

INTERROGATING EQUITY: A DISABILITY JUSTICE APPROACH TO GENETIC ENGINEERING

My contribution to the summit draws on ten years of research on the social impact and meaning of emerging biotechnologies, in particular regenerative medicine and genomics, in which I have examined the relationship between innovation and equity as it relates to socio-economic class, gender, race/ethnicity, citizenship, and disability. In what follows, I will focus primarily on disability with the understanding that these forms of social stratification, and their intersection with science and technology, are inextricably connected. With that, my intervention is twofold.

First, I would like to highlight that the distinction that is commonly made between genetic therapy and enhancement is not at all straightforward or stable. The bright line we may wish to draw between laudable and questionable uses of gene editing techniques is more porous than we realize. Many practices that were optional yesterday are medicalized today. Likewise, traits and behaviors that we may regard as "enhancement" today may very well find a therapeutic justification tomorrow. As the disability studies scholar Tom Shakespeare commented, "To fix a genetic variation that causes a rare disease may seem an obvious act of beneficence. But such intervention assumes that there is robust consensus about the boundaries between normal variation and disability." Indeed, there is not, even though that distinction has become ubiquitous in reporting on gene editing.

The second point is this: Questions of equity and justice as they relate to human gene editing and related fields should not be mistaken as a kind of "special interest" or simply another angle from which to approach these topics or even solely a "problem" to be overcome. But rather, the work of interrogating equity serves as a vital framework for democratizing science more broadly because of the way it causes us to wrestle with some of the foundational assumptions of biotechnology, to the extent that we take up the challenge. I will briefly elaborate on these two points below, but first some background on the empirical basis of my comments.

In 2005 I began researching the passage and implementation of California's Stem Cell Research and Cures Initiative. Proposition 71, as it was commonly known, successfully passed in November 2004, becoming the largest single source of stem cell funding in the world, authorizing the sale of state bonds in the amount of $3 billion to be managed by a new stem cell agency and governed by the Independent Citizens' Oversight Committee. This unprecedented state investment is protected by a new constitutional "right to research" amendment that requires a 70% legislative super majority to modify, and it is this context of a political right to scientific inquiry that I used as a window to analyze the relationship between innovation and equity more broadly. I conducted a two year mixed-method study of the Initiative, and through a formal affiliation with the state agency as part of its first cohort of training fellows, I conducted interviews with key proponents and opponents of the Initiative, as well as people affected by conditions that could potentially be treated by stem cell therapies. I also produced a mixed archive of documents and media that allowed me to analyze the contours of social inclusion and exclusion.

One of my observations throughout this process was that to the extent that non-scientists were involved, a particular subset of patient advocates were positioned as the

"default public" to whom the new state apparatus was most accountable. And although patient advocates hold a wide variety of perspectives on these issues, those that were most vocal in the California context framed their demands in terms of medical consumer rights, or what scholars have dubbed an "upwardly tilted public agenda" that appeals to middle-class supporters. Such advocacy is unlikely to represent the vast majority of disabled people for whom dismantling policies and prejudices that cast them as second class is often more vital than access to "miracle cures." The fact is that innovation and inequity too often go hand-in-hand. Social science research piled high shows that as we develop the capacity to control disease and death, the benefits go disproportionately to those who already monopolize resources. So we either decide to prioritize issues of equity and justice early and often, or we ensure a world in which the health and longevity of some are predicated on the disposability of others.

In order to fully "interrogate equity," we must foster deliberation that moves beyond questions of access to treatment, however important, and think very seriously about the design of research—who does it and with what guiding questions and assumptions, because how research is framed is never neutral, universal, or inevitable. Gene editing techniques are seeded with values and interests—economic as well as social—and without careful examination, they will easily reproduce existing hierarchies, including ableist assumptions about which lives are worth living and which are worth "editing" out of existence.

In the words of geneticist James Watson, "From this perspective seeing the bright side of being handicapped is like praising the virtues of extreme poverty. To be sure there are many individuals who rise out of its inherently degrading states. But we perhaps most realistically should see it as the major origin of asocial behavior." This statement reflects the default setting of much biotechnology—a benevolent medical missionary ethos that says essentially "We know what you need better than you do." For this reason it is crucial that we take the disability justice refrain "Nothing About Us, Without Us" seriously, noting also that there is substantial stratification among disabled people. And in the same way we do not expect scientists from a single field to address all the technical complexity associated with gene editing, surely we need to be equally attentive to social complexity, so that white middle-class patient advocates do not continue to serve as the default public to whom science and technology is accountable.

These were among the issues discussed at a National Convening on Disability Rights and Genetic Technologies, where participants noted that, of course, "Some people with disabilities eagerly await gene therapies. But many people are concerned that the increasing use of genetic technologies in this context reflects and reinforces societal assumptions that disability is always harmful and should be prevented." The concern here is that people with disabilities would be less valued at a societal level as genetic technologies become more common, especially in the absence of public education and media campaigns on disability and genetics. In a similar vein, commenting on the 2015 International Gene Editing Summit, biochemist and disability scholar Gregor Wolbring explained, "The disability-rights community has a history of disagreement with scientific and clinical experts over their perception of people with disabilities. This is summarized as ableism, a view that disability is an abnormality instead of a feature of human diversity. It can lead to flawed 'solutions' and disempower those affected."

So then, how do we reflect carefully on ableist norms that are often embedded in genetic technologies? I will briefly flag five ways we routinely constrict what counts as relevant and meaningful to scientific innovation.

The first is an *ahistorical fallacy*, which is the tendency to project forward in time without the temporal corollary—a careful reflection on historical precedents and processes. Too often the contours of our thinking mirror the hyperbolic rhetoric of science—"breakthrough," "cutting edge," "breath-taking," and "miraculous," leading us to overlook continuities as we train our attention on all that appears novel. My observations at a number of meetings such as this is that those seeking to dismiss the need to interrogate equity do so by assuming a hard break between past harms and future possibilities.

The second is a *legalistic fallacy* when we assume that reforming policies and laws is sufficient to shaping the context of science for the greater good. The passage of the Genetic Non-Discrimination Act, for example, was necessary but not sufficient to ensure that genetic predisposition to illness will not result in employer or insurance bias. That is, legal change must go hand-in-hand with public engagement and deliberation well beyond the staging of a single summit.

The third way we routinely constrict our ethical imagination is an *informed fallacy* when we presume that standard approaches to informed consent are sufficient in arenas that are characterized by so much scientific and medical uncertainty. The best that researchers can really promise is a partially informed consent—so that we urgently need to re-think and re-invest in technologies of trust and reciprocity that address the many uncertainties involved.

The fourth is a *fixed fallacy*, which is the tendency to assume that the way in which scientific harms get enacted in the present will look the same way they did in the past, rather than mutating with the times. This fallacy has us look for examples of state-sponsored eugenics, for example, overlooking the way that market logic puts the responsibility of "racial fitness" in the hands of the consumer. In this way, the fixed fallacy serves as a counterweight to the ahistorical fallacy, by alerting us to the mercurial and often "liberal" context in which individual choices reinforce oppressive hierarchies.

The fifth and final way we may inadvertently constrict our ethical imagination with respect to genetic engineering is the *euphemistic fallacy*, which is the tendency to adopt language that is already seeded with a particular ethical perspective on the techniques in question. The word "editing" itself sounds benign and even beneficial. Whereas for those struggling against the many forms of stigma and marginalization that grow out of ableist norms, editing may be more akin to being pushed through a shredding machine.

In moving forward, then, there are many ways to expand our scientific and ethical imagination. First, we need to remain watchful of how safeguarding "medical consumer freedom" displaces many other concerns. It is not coincidental that this notion of medical choice goes hand-in-hand with competitive chants of winning a global scientific race. As renowned legal scholar Patricia Williams noted with respect to CRISPR, "What's going on now is also a rat race to beat out others in the charge to the patent office. Hence, much of this has an urgency to its framing that exploits our anxiety about mortality itself. Hurry up, or you'll die of an ugly disease! And do it so that "we" win the race—for everything's a race. A race against time. A race to file patents. A race to market. A race to better babies, better boobs. There is never enough glory or gain, there is always the moving goal post." The rhetoric of urgency, in other words, is not neutral or inherently good.

An expansive approach to genetic technologies, one that avoids the many fallacious constrictions I have outlined above, is one that includes disabled people "at the table and not

just on the table of the life sciences." The insights and expertise of those who have been harmed and exploited in the name of progress offer us a more rigorous foundation by which to democratize science than the current model in which citizens are imagined to be "We, the patients" waiting for the fruits of science to ripen. To begin this shift, we must become just as inventive about addressing social complexity as we are about biological complexity. If our bodies can regenerate, let us not imagine our body politic as so utterly fixed.

Recommended Reading

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