KEVIN FINNERAN

Responding to CRISPER/Cas9

The prospect of influencing the course of human evolution through technological intervention has been thought about for a long time, but usually in an abstract or theoretical way. But that possibility has become an impending reality at a breathtaking pace in the past few years. Jennifer Doudna and Emmanuelle Charpentier published a paper in *Science* in June 2012 that demonstrated that CRISPR/Cas9 (if you must know, clustered regularly-interspaced short palindromic repeats, with CRISPR associated protein 9) is a remarkably accurate and relatively easy-to-use tool for editing genes. In October Feng Zhang of the Broad Institute published a paper in *Science* that demonstrated that CRISPR could be used to edit mammalian genes. Soon after, George Church of Harvard published a paper demonstrating the use of CRISPR in human cells. Excitement spread quickly through the scientific community as researchers realized that this new capability opened doors to a mind-boggling array of new directions for research.

With the thrill of new possibilities came a chill of recognition that there is no guarantee that all the new uses of this technology would be benign. A group of scientists, including leaders in field such as Jennifer Doudna and a few veterans of the 1975 Asilomar Conference at which a group of scientists debated the wisdom of pursuing the possibilities opened by the development of recombinant DNA technology, met in January 2015 to discuss the potential risks associated with this new gene-editing technology. In March 2015 they published an article in *Science* that asked whether it would be wise to place voluntary restrictions on the use of CRISPER/Cas9 until we had a better understanding of how it might be used. They recommended that leading thinkers in science, medicine, law, ethics, and policy come together to discuss how to proceed.

The members of this group approached a number of institutions to see who would be interested in convening this discussion. Not surprisingly, the National Academy of Sciences (NAS) and National Academy of Medicine (NAM) were among those who were approached. After a frantic round of discussions among leaders of the scientific community and a number of institutions, there was agreement that the Academies were in the best position to organize the event, and NAS president Ralph Cicerone and NAM president Victor Dzau formed an advisory group to guide the effort.

Everyone understood from the outset that this must be an international discussion, and the U.S. academies' leaders reached out to engage their counterparts at academies in other countries. The advisory group included representatives of the Royal Society of the United Kingdom and the Chinese Academy of Sciences. The advisory group decided that two types of activities were needed. There had to be a rigorous study by an expert committee to collect as much information as possible about the technology and to develop a well-considered assessment of the risks as well as the opportunities.

In addition, the advisory group recognized that news of this technology was spreading fast and raising understandable public concern. The U.S. House of Representatives' Science Committee organized a hearing so that they could learn from experts about the possible implications. The advisory group decided that the public and policy makers did not want to wait a year or more for an expert committee to deliberate and then announce its conclusions. The repercussions of this technology are potentially so powerful and so widespread that it was necessary to include a much wider range of perspectives and to do so as quickly as possible.

NAS and NAM decided to host a large meeting at their headquarters in Washington, DC. The Royal Society and Chinese Academy of Sciences agreed to cosponsor the event. The advisory committee then

DANIEL KOHN
Instance of a DataSet, 2013
Panels from Floor 6 installation

appointed a planning group to organize what would become the Summit on Human Gene Editing. They chose David Baltimore—Nobel laureate, Asilomar veteran, participant in the January Palo Alto meeting, and lead author of the *Science* article—to chair the planning committee. Other members included scientists, physicians, and experts in law, ethics, regulation, and policy from several countries. Although gene-editing advances will have a powerful impact throughout the life sciences and will be applied to plants and animals, the advisory committee decided to focus its attention on the use of the technology with human somatic and germline cells because of the broad public interest in this aspect, and to keep the boundaries of discussion manageable.

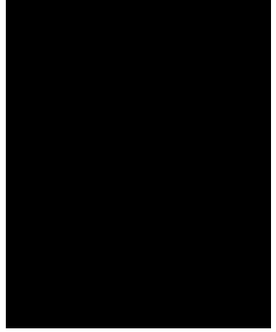
The committee began meeting in August 2015 to put together the Summit, which would be held December 3-5. They designed an agenda that included an overview of the science explained by the leading researchers in the world, but that devoted most of its attention to the relevant social, legal, ethical, and policy questions that are essential to understanding how to use or limit this technology. There were speakers from about 20 countries and representatives of many of the world's scientific academies. Roughly 75 reporters attended the meeting. Participation was open to the public, and registration quickly reached the maximum of 400 people. The entire meeting was webcast and attracted viewers from 70 countries.

The event was recorded and is available for viewing on the National Academies website. To provide a glimpse of the meeting, *Issues* is publishing the text of presentations by David Baltimore, Alta Charo, Daniel Kevles, and Ruha Benjamin that were made at the Summit. They provide a taste of the quality of the speakers and the remarkable range of topics and perspectives that were circulating during the Summit. On the website, one can find the text of additional presentations plus a statement from the organizing committee on what it learned during the Summit.

There was never any presumption that the Summit would resolve any of the debates. Its purpose was to illustrate the importance of the subject, the variety of voices that need to be at the table, and the need to stimulate discussions across disciplines, cultural and ethical traditions, and national boundaries. We are just at the beginning of coming to terms with a new generation of genetic technology and knowledge that will continue to advance and open new doors.

As a first step in extending the discussion, we include an article by Henry Miller, who argues that the Summit was an unnecessary impediment to the progress of the science and its ultimate use to treat human disease. No doubt there are others who will argue that scientific hubris has already exceeded the boundaries of what society can countenance, that the Summit was a ploy to enable scientists to control the discussion and the ultimate fate of the technology.

The reality is that nothing is decided yet. The study committee organized by the U.S. National Academies is hard at work; similar committees are meeting in other countries; public discussions are taking place across the globe; and we can expect to see future summits that assemble participants from around the world. In its starkest and most dramatic form, new genetic technology offers the prospect of humanity taking control of the direction of its own evolution. If that doesn't give you something to think about, nothing will.



DANIEL KOHN
Panels from *Red 1–9* , 2009

DAVID BALTIMORE

Why We Need a Summit on Human Gene Editing

In 1981, Matthew Meselson pointed out that the puzzle brought to light by Darwin, of what constitutes heredity, was solved in two tranches. The first lasted from 1900, when Mendel's work of the last half of the nineteenth 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?

Thus, we are part of a historical process that dates from Darwin and Mendel's work in the nineteenth century. We in the scientific community 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, 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.

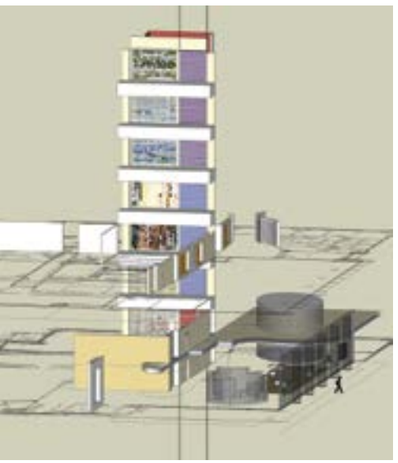
Although these new technologies offer unprecedented opportunities for advancing science and treating disease, the group recognized that they might be used prematurely or in ways that might be viewed as inappropriate. Because of these concerns, those at the Napa meeting offered a number of recommendations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

The National Academies of Sciences and Medicine agreed to convene an International Summit on Human Gene Editing and asked me to chair the

Daniel Kohn

As artist in residence at the Broad Institute in Cambridge, Massachusetts, Daniel Kohn noticed that the walls were a vital communications medium. Announcements, meeting minutes, cellular diagrams, equations, and cartoons were pasted everywhere. He realized that the walls would be the perfect place for the art he would create as a response to his cross-disciplinary interactions with the Broad scientists. He was granted use of the valuable real estate opposite the elevators on each floor.

Over several years Kohn produced a number of oil paintings plus *Instance of a DataSet*, a collection of installations of archival inket prints on Hahnemuhle rag paper, mounted on 10.25-inch aluminum panels, and hung on a cable grid. Each uses color, imagery, and careful arrangement to capture some aspect of the work taking place in the building. The works are static, but Kohn also wanted to do something to capture the process of science in which researchers are always building on, refining, and interacting with the work of their predecessors. He created Assembly Space, an app version of each of his grids that allows users to rearrange the elements in the grid to create their own versions and to save them on the site.



"The idea I had coming into this was that, just like when you're working in a scientific environment, it's not a solitary pursuit. Ideas go into the space of collective thinking—they circulate, get published, and get shared," Kohn said of the project.

Kohn is currently artist in residence at the Center for Epigenomics at Albert Einstein College of Medicine, in the Bronx, New York and recently founded the Art Science Observatory, a new organization dedicated to enabling research across art and science. Kohn is represented by Cynthia Reeves Gallery in New York and New Hampshire. Visit the artist's website at www.kohnworkshop.com.

planning committee. When the committee began its preparations, 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.

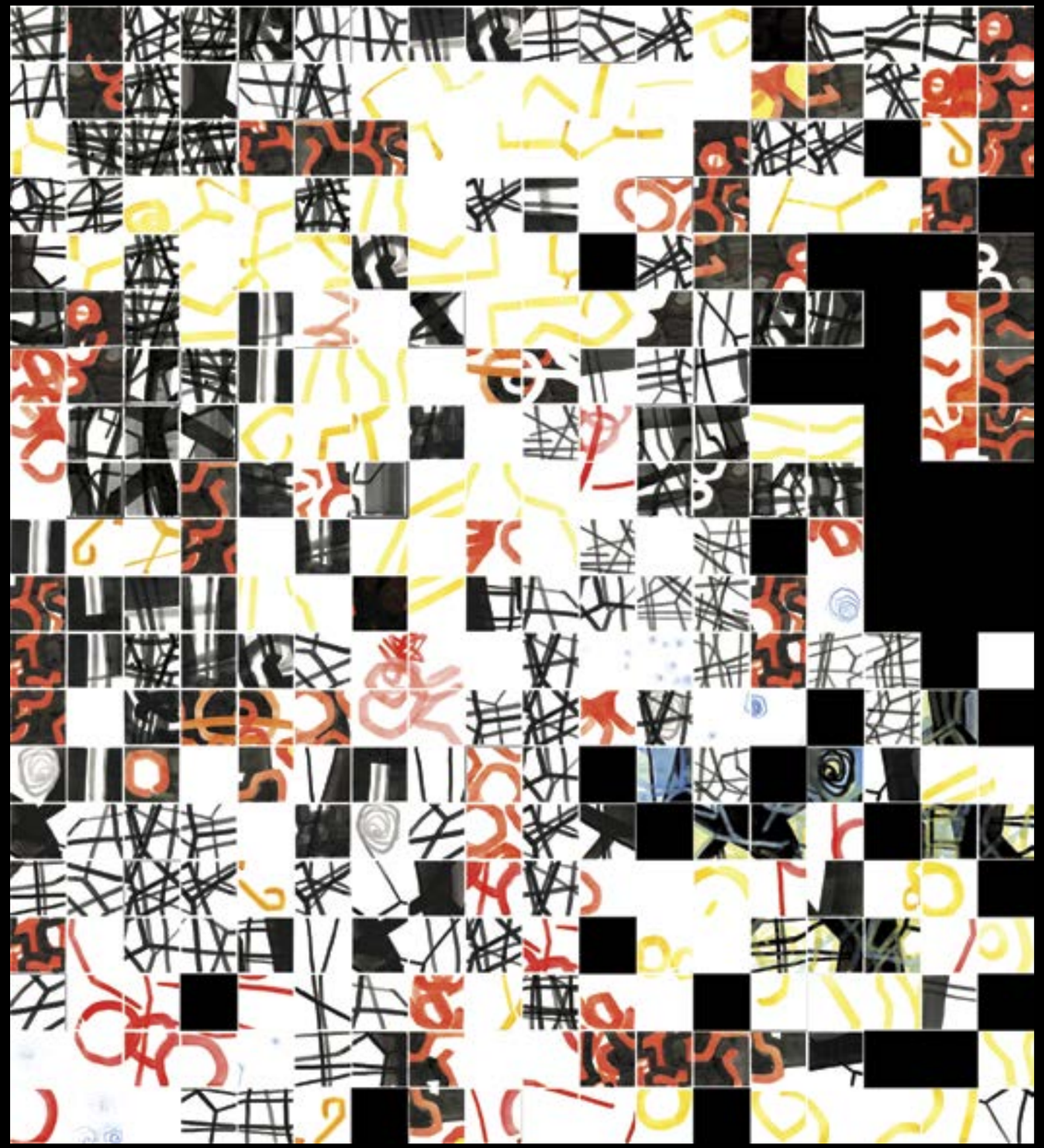
The committee was also aware that there are numerous relevant concurrent projects under way, both within the U.S. National Academies and in the larger community of stakeholders. These include two U.S. National Academies studies, one on gene drive in non-human organisms and the other on genetic modification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

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.

The Summit should be seen as an opportunity to launch a much broader public discussion. It is part of a larger effort to inform policy makers 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.

We are saying that this is something to which all



DANIEL KOHN, *Instance of a DataSet*, Month 9 (Floor 1), 2013

Opposite: Panels from Floor 1 installation and architectural rendering of plan for the multi-floor commission at the Broad Institute.

DANIEL KOHN, *BlueMol 1–9*, 2009
Oil on canvas, [size?]
Below: Lobby of the Broad Institute.

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 advisers 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 to 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 has 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. At the Summit, individuals sent blogs, tweets, and retweets as the discussion was taking place. The entire event was webcast around the world, and the video is available online for all to see.

This Summit incorporated many themes and many perspectives, but the overriding question was when, if ever, will we want to use this gene-editing technology. 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 allowed to use editing for genetic enhancement purposes?

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

David Baltimore is president emeritus and Robert Andrews Millikan Professor of Biology at Caltech. He chaired the planning committee for the International Summit on Human Gene Editing.

R. ALTA CHARO

The Legal and Regulatory Context for Human Gene Editing

The potential use of human gene editing is stimulating discussions and responses in every country. I will attempt to provide an overview of legal and regulatory initiatives around the globe. But I need to note that we are talking not only about government when we talk about law, regulation, and biotechnology. We are really talking essentially about an ecosystem that is made up of government, the public, and private industry, which produces innovative products based on the basic science and applied research coming out of our universities.

The ecology of this system is one in which there are many legal or policy issues that combine to affect whether biotechnology is promoted or hindered in any particular country. It ranges from topics such as intellectual property rights, which are reflected in areas from 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 and under what conditions. The regulatory framework is going to determine the speed at which biotechnology moves from laboratory to development to marketed product.

The consumer demand will also be a profoundly important feature in determining which products are developed, because so many discoveries 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 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 a country is 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, the United States has a fairly permissive approach to biotechnology applied to genetically engineered animals and plants in the agricultural sector, whereas it has a much more cautious approach when it comes to the use of 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. There can be differences among countries and even 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, strong patent protection can be viewed as promotional because it gives industry the greatest possible financial incentive to pursue 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.

In the area of biosafety, we see more case-by-case evaluation of biotechnology products, where everything really begins to hinge simply on the

presumption about risk. One can take a precautionary approach that presumes it is dangerous until it is proven safe, or a permissive approach that presumes it is safe until it is proven dangerous. Since it is often impossible to prove either danger or safety, where that presumption falls will often be more determinative than anything else in deciding how quickly technologies move from the 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 (FDA) has approved the sale of a genetically modified farmed salmon, there is a debate about whether that salmon has 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 could be setting ourselves up for a more precautionary regulatory approach because it will tie into public attitudes that are often based on concern about either the corporate influence or the actual underlying science. On the other hand, if regulation is mandated only when there is evidence of a higher level of risk, products will reach the market more quickly, reflecting a more promotional stance.

To implement any one of these approaches, we have a variety of mechanisms that range from the least to the most enforceable. Public consultation is the least enforceable approach, and there is a spectrum of regulatory and legislative measures that can strengthen the level of control.

In the area of public consultation, we have 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 catchword 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 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, formed a royal commission on new reproductive technologies that held hearings on the topic across the country. In the European Union (EU), genetically engineered foods, or GMOs as they are 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 centralized directive 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 thereby alter the direction or the speed of biotechnology innovation.

Next in this hierarchy of enforceability comes voluntary self-regulation. The 1975 Asilomar conference on recombinant DNA technology was one of the more notable examples of voluntary self-regulation by the scientific community when it recognized that there were certain risks that needed to be investigated before it pushed forward at full speed. The research community voluntarily imposed on itself moratoria on certain applications and implemented a series of precautionary measures having to do with containment of possibly dangerous materials. A more recent example is the set of 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 instances of self-regulation is that unlike the government-imposed rules, these were truly self-imposed rules that were seriously constraining in many ways. They often called for prohibiting payment for certain materials and services in ways that limited the ability of the scientific community to move as quickly as it might want. For example, it limited the use of chimeras and established strict guidelines on the distribution of the gametes and embryos needed for research.

It was a success in the sense that it forestalled what might have been really onerous government action at the state or federal levels, and it demonstrated that self-regulation could be flexible and nuanced without sacrificing reliability. The self-regulatory approach has also been used in the case of "gain of function research," a very awkward name for research that increases the pathogenicity, transmissibility, or resistance to countermeasures of known pathogens.

Interestingly, these kinds of voluntary self-regulatory activities often lead directly into some government adoption by proxy of much of the

Opposite:
DANIEL KOHN
Instance of a DataSet, 2013
Panels from Month 1 (Floor 4)

content of the 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, which collaborates with its counterparts around the world to manage situations where there is fear that publishing key data will facilitate the transformation of useful biotechnology into bioterrorism.

There are government guidelines in other areas as well. These provisions 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 guidelines, they are not going to run afoul of some actual regulation or law. These guidelines also create strong social norms.

At the international level, there is the Council for International Organizations of Medical Sciences (CIOMS), which is very influential in creating global standards for research on human subjects. It refers back specifically to the Nuremberg protocols and has the ability to be more restrictive than any particular national set of rules.

That doesn't mean that national laws will necessarily follow, but it establishes a norm from which nations feel free to deviate only when they can provide justification that it is necessary to achieve some public benefit. Therefore, the CIOMS 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 it legally in the United States, but 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—that is, the detailed administrative rules adopted pursuant to legislative direction and authority—has the ability to be much more responsive and detailed, and is influenced to a greater extent 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 challenges for democratic systems.

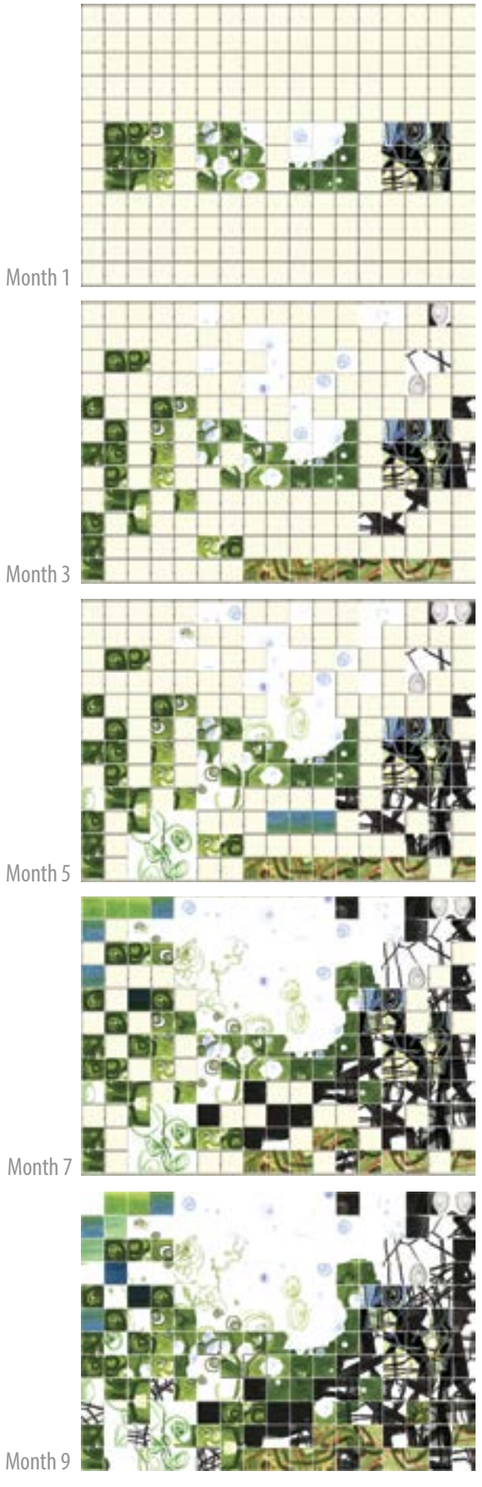
Focus on human gene therapy

Looking specifically at regulation of human germline modification, a 2014 survey of 39 countries by Motoko Araki and Tetsuya Ishii found a variety of regulatory approaches. Many European countries legally prohibit any intervention in the germline. Other 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.

There are international instruments that have been written at various levels to address aspects of genetics. For example, the Council of Europe's Oviedo Convention 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 later generations. It builds on earlier European conventions.

But like many international instruments, it is not ratified by every member country and, even when ratified, has not necessarily been 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 treats it as a biological drug or a device, depending on its mode of operation. It comes under the comprehensive regulation of the FDA and under multiple laws focusing on infection control, efficacy, and safety.



DANIEL KOHN, *Instance of a DataSet*, Floor 6, 2013

The seven floor installations at the Broad Institute were developed monthly over a period of nine months. Evolution of the Floor 6 installation is shown at left.

Opposite: Floor 6 installation in progress.

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

But what is perhaps distinctive about the United States is that although it has very strong controls in the pre-market stage of these technologies, once a drug, device, or 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, population, or dosage. There are some post-market mechanisms to track the quality of this work and to dial it back, but they are not as strong as in other countries.

Gene therapy in South Korea has a pathway very similar to the one in the United States. Interestingly, South Korea has come to have a focus on innovation, with 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 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 the market. Many other countries are also considering adopting some form of conditional approval.

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

The EU has also added special provisions for advanced therapy medicinal products. Gene therapy is almost certainly 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 from the beginning as equally dangerous and runs every proposed drug through the same paces of testing for safety and efficacy. By contrast, in Japan, one will 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 recently added a conditional approval pathway specifically for regenerative medicine and gene therapy products. It will be very interesting to see how this operates. It is still new, so the experience is 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. In the United States, the death in 1999 of Jesse Gelsinger in a gene therapy trial at the University of Pennsylvania set back the field by years.

One of the challenges with the conditional therapy pathway is to balance the desire to move forward as quickly as possible while avoiding the kinds of adverse outcomes that not only injure individuals, but could slow progress to the point that many individuals who could have benefited in the future are denied the technology because it is delayed so significantly.

Singapore has a risk-based approach similar to Japan's. What is interesting in Singapore is that it actually tries to figure out what would be a high- versus low-risk intervention in the area of cell therapy. The variables that are used include whether the manipulation is substantial or minimal, whether the intended use is homologous or non-homologous, and whether it will be combined with a drug, a device, or another biologic.

The only consideration one might add is autologous versus non-autologous use. In Singapore, these distinctions are used to classify the level of risk. In the United States, it is used to determine if the FDA has the jurisdiction 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, 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 the patenting of human biological materials. Together they are 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.

Product or process?

There is a fundamental divide in the world about how we regulate biotechnology that goes beyond the categories of promotional, permissive, or prohibitive. It is whether we think of biotechnology as a thing unto itself, or whether we think of it simply as one more tool that goes into making various products.

If one regulates the technology, one regulates everything about the technology in a comprehensive way. An example is the EU's community strategy, which takes a global approach to the technology that makes it easier for the public to understand the so-called "laws on biotechnology." One can focus on key aspects of the science that create key questions about the effects of a particular kind of innovation. Itto makes it possible 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 on 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 for others the impact will be confined to a single individual or a single animal.

Regulating by product gives one the advantage of being able to be much more specific about the degree of risk that is feared or anticipated, and the degree of caution needed, as well as being able to take advantage of mature degrees of expertise in the regulatory pathways appropriate for drugs, foods, and pesticides, and of 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, and so on. To many people, this sounds as if the country is not regulating biotechnology, and it creates the possibility for unintended or even unnoticed gaps among these laws or conflicts among them.

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 where in the R&D process we want to exercise control. Pre-market control is truly important to avoid the devastating adverse events that can occur if we move too quickly. But if 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 earlier is made by a company that has reportedly been on the verge of bankruptcy during the 20-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 wound up abandoning this project, in part because that pathway was so long, slow, and expensive. There is a cost to pre-market controls that are so strong that they drive out the small, and often very creative, innovators.

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

Finally, harmonization across national borders is 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 lesson with the many conflicts among jurisdictions in the area of embryonic stem cell research.

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.

Innovation is not something that is 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.

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DANIEL J. KEVLES

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 President Barack Obama's science adviser John Holdren has 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 twentieth 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 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 twentieth 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 non-coercive means of multiplying the desirables. Galton proposed that the state sponsor competitive examinations in hereditary merit, celebrate

the blushing winners in a 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 its 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 letter carrier 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 eugenicists 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 6 million Jews—their ultimate undesirables—into the death camps.

Postwar developments

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

DANIEL KOHN, *Instance of a DataSet*, Month 9 (Floor 2), 2013

This page and opposite: Panels and Floor 2 installation at the Broad Institute.

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 improvement of the genetic profile in succeeding generations.

During the first third of the twentieth century, hundreds of men and women wrote to the Eugenics Record Office, in 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

DANIEL KOHN, *Instance of a DataSet*, Floor 2, 2013

This page and opposite: Panels from Floor 2 installation at the Broad Institute.

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 germline 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, 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 germline 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 reproductive technology. 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.

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DANIEL KOHN, *Instance of a DataSet*, 2013

Panels from Month 1 installation configurations: Floor 2 (top) and Floor 3 (bottom) at the Broad Institute.

RUHA BENJAMIN

Interrogating Equity: A Disability Justice Approach to Genetic Engineering

My approach to human genetic engineering draws on 10 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 connects to socioeconomic class, gender, race and 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 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 nonscientists 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.

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 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 that there is substantial stratification among disabled people. And in the same

DANIEL KOHN
Veiws of the Broad Institute commission, including *Instance of a DataSet*, 2013, and *Sets and States*, 2009.

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 the 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 Summit on Human Gene Editing, 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."

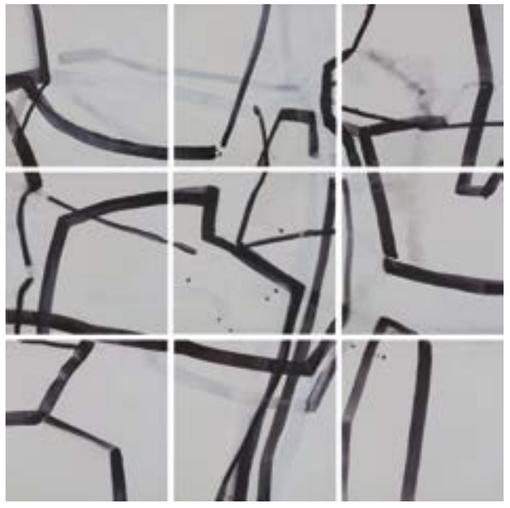
So then, how do we reflect carefully on ableist norms that are often embedded in genetic technologies? I will briefly flag five ways we routinely constrict what counts as relevant and meaningful to scientific innovation.

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," "breathtaking," 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 Summit 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

DANIEL KOHN, *BlackMol 1–9*, 2009
Oil on canvas, [size?]

Above: Lobby of the Broad Institute.



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 instance, 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 outlined earlier in this article, 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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On Human Gene Editing

International Summit Statement by the Organizing Committee

Scientific advances in molecular biology over the past 50 years have produced remarkable progress in medicine. Some of these advances have also raised important ethical and societal issues—for example, about the use of recombinant DNA technologies or embryonic stem cells. The scientific community has consistently recognized its responsibility to identify and confront these issues. In these cases, engagement by a range of stakeholders has led to solutions that have made it possible to obtain major benefits for human health while appropriately addressing societal issues.

Fundamental research into the ways by which bacteria defend themselves against viruses has recently led to the development of powerful new techniques that make it possible to perform gene editing—that is, precisely altering genetic sequences—in living cells, including those of humans, at much higher accuracy and efficiency than ever before possible. These techniques are already in broad use in biomedical research. They may also enable wide-ranging clinical applications in medicine. At the same time, the prospect of human genome editing raises many important scientific, ethical, and societal questions.

After three days of thoughtful discussion of these issues, the members of the Organizing Committee for the International Summit on Human Gene Editing have reached the following conclusions:

1. Basic and Preclinical Research. Intensive basic and preclinical research is clearly needed and should proceed, subject to appropriate legal and ethical rules and oversight, on (i) technologies for editing genetic sequences in human cells, (ii) the potential benefits and risks of proposed clinical uses, and (iii) understanding the biology of human embryos and germline cells. If, in the process of research, early human embryos or germline cells undergo gene editing, the modified cells should not be used to establish a pregnancy.

2. Clinical Use : Somatic. Many promising and valuable clinical applications of gene editing are directed at altering genetic sequences only in somatic cells—that is, cells whose genomes are not transmitted to the next generation. Examples that have been proposed include editing genes for sickle-cell anemia in blood cells or for improving the ability of immune cells to target cancer. There is a need to understand the risks, such as inaccurate editing, and the potential benefits of each proposed genetic modification. Because proposed clinical uses are intended to affect only the individual who receives them, they can be appropriately and rigorously evaluated within existing and evolving regulatory frameworks for gene therapy, and regulators can weigh risks and potential benefits in approving clinical trials and therapies.

3. Clinical Use: Germline. Gene editing might also be used, in principle, to make genetic alterations in gametes or embryos, which will be carried by all of the cells of a resulting child and will be passed on to subsequent generations as part of the human gene pool. Examples that have been proposed range from avoidance of severe inherited diseases to 'enhancement' of human capabilities. Such modifications of human genomes might include the introduction of naturally occurring variants or totally novel genetic

changes thought to be beneficial.

Germline editing poses many important issues, including: (i) the risks of inaccurate editing (such as off-target mutations) and incomplete editing of the cells of early-stage embryos (mosaicism); (ii) the difficulty of predicting harmful effects that genetic changes may have under the wide range of circumstances experienced by the human population, including interactions with other genetic variants and with the environment; (iii) the obligation to consider implications for both the individual and the future generations who will carry the genetic alterations; (iv) the fact that, once introduced into the human population, genetic alterations would be difficult to remove and would not remain within any single community or country; (v) the possibility that permanent genetic 'enhancements' to subsets of the population could exacerbate social inequities or be used coercively; and (vi) the moral and ethical considerations in purposefully altering human evolution using this technology.

It would be irresponsible to proceed with any clinical use of germline editing unless and until (i) the relevant safety and efficacy issues have been resolved, based on appropriate understanding and balancing of risks, potential benefits, and alternatives, and (ii) there is broad societal consensus about the appropriateness of the proposed application. Moreover, any clinical use should proceed only under appropriate regulatory oversight. At present, these criteria have not been met for any proposed clinical use: the safety issues have not yet been adequately explored; the cases of most compelling benefit are limited; and many nations have legislative or regulatory bans on germline modification. However, as scientific knowledge advances and societal views evolve, the clinical use of germline editing should be revisited on a regular basis.

4. Need for an Ongoing Forum. While each nation ultimately has the authority to regulate activities under its jurisdiction, the human genome is shared among all nations. The international community should strive to establish norms concerning acceptable uses of human germline editing and to harmonize regulations, in order to discourage unacceptable activities while advancing human health and welfare.

We therefore call upon the national academies that co-hosted the summit—the U.S. National Academy of Sciences and U.S. National Academy of Medicine; the Royal Society; and the Chinese Academy of Sciences—to take the lead in creating an ongoing international forum to discuss potential clinical uses of gene editing; help inform decisions by national policymakers and others; formulate recommendations and guidelines; and promote coordination among nations.

The forum should be inclusive among nations and engage a wide range of perspectives and expertise—including from biomedical scientists, social scientists, ethicists, health care providers, patients and their families, people with disabilities, policymakers, regulators, research funders, faith leaders, public interest advocates, industry representatives, and members of the general public.