International Summit on Human Gene Editing: A Global Discussion

DETAILS

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MEETING IN BRIEF
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COMMITTEE ON SCIENCE, TECHNOLOGY, AND LAW
POLICY AND GLOBAL AFFAIRS

International Summit on Human Gene Editing
A Global Discussion

New biochemical tools have made it possible to change the DNA sequences of living organisms with unprecedented ease and precision. These new tools have generated great excitement in the scientific and medical communities because of their potential to advance biological understanding, alter the genomes of microbes, plants, and animals, and treat human diseases. They also have raised profound questions about how people may choose to alter not only their own DNA but the genomes of future generations.

To explore the many questions surrounding the use of gene editing tools in humans, the U.S. National Academy of Sciences, the U.S. National Academy of Medicine, the Royal Society, and the Chinese Academy of Sciences hosted a three-day international summit on December 1-3, 2015, in Washington, DC. The summit brought together more than 500 people from around the world for three days of presentations and deliberations on the scientific, ethical, legal, social, and governance issues associated with human gene editing, while an additional 3,000 people watched the summit online.

"We could be on the cusp of a new era in human history," said David Baltimore (California Institute of Technology), chair of the summit organizing committee, in his opening remarks. "Today, we sense that we are close to being able to alter human heredity. Now we must face the questions that arise. How, if at all, do we as a society want to use this capability? This is the question that has motivated this meeting."

This brief summary should not be seen as representing the conclusions of the summit as a whole. Rather, it highlights some of the observations made during the event in order to provide background for the statement issued by the organizing committee in the summit's final session.

Rapidly Improving Tools

As Klaus Rajewsky (Max Delbrück Center for Molecular Medicine) pointed out, the new gene editing tools are the product of more than 60 years of fundamental research into the molecular nature of DNA molecules. Previous technologies using molecules known as zinc finger nucleases and TALENs had made it possible to alter DNA at targeted locations. While these technologies are currently being used in clinical trials, they are cumbersome and difficult to use. A new technique using a molecular assemblage known as CRISPR-Cas9, which arose out of research into how bacteria protect themselves from viral infection, is simple, inexpensive, and can target DNA sequences with great specificity. "The system is so overwhelmingly efficient and specific that it is changing our entire outlook for future gene editing," said Rajewsky.

Despite its capabilities, CRISPR-Cas9 still has deficiencies, observed Jin-Soo Kim (Seoul National University/Institute for Basic Science). It can alter DNA at locations other than the target, which could inactivate essential genes, activate cancer-causing genes, or cause chromosomal rearrangements. It can change the DNA in some cells but not all, resulting in a mosaic of altered and unaltered cells. It can generate immune responses if introduced into the body. Many drugs cause off-target effects but are still effective, Kim added. Nevertheless, the CRISPR-Cas9 system is still undergoing development to reach the level of safety where it could be used in clinical applications.

Methods to identify genome-wide off-target effects could help assess the safety and efficacy of these new tools, said J. Keith Joung (Massachusetts General Hospital and Harvard Medical School). Also, as Jennifer Doudna (University of California, Berkeley) and Emmanuelle Charpentier (Max Planck Institute

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"..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."

David Baltimore, Caltech

The National Academies of
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for Infection Biology) pointed out, gene-editing techniques are being rapidly improved to increase their specificity and reduce off-target effects. According to Bill Skarnes (Wellcome Trust Sanger Institute), "I am almost certain that we will realize the potential of precision medicine in the next five years, where we can modify any base or make any genetic modification we please to model [or] correct disease."

A Wide Range of Applications

Several presenters at the summit stated that the most immediate impact of the new gene editing techniques has been on basic biological and biomedical research. CRISPR-Cas9 is being used in laboratories around the world to understand the mechanisms of action of genes, proteins, and cells. It is being used to study the differentiation of human sperm and egg cells, fertilization, cell division, and embryonic development. It is creating new knowledge on everything from the gene editing techniques themselves to complex human diseases.

Potential applications of gene editing techniques in humans can be divided into two categories. In the first category are changes to DNA in human somatic cells, which constitute most of the cells of the human body, including the cells that make up the blood, muscle, internal organs, skin, bone, and connective tissue. In ex vivo gene editing, CRISPR-Cas9 or another molecule is used to alter, delete, or add DNA, or modify the expression of genes, in cells that are extracted from the body or grown in culture. With in vivo approaches, gene editing molecules are introduced into the body where they target cells for DNA alterations.

At the summit, presenters listed a wide variety of possible applications of somatic cell gene editing. For example, zinc finger nucleases already have been used to alter the CCR5 gene of T cells in blood extracted from people infected with HIV, explained Fyodor Urnov (Sangamo BioSciences). When reinfused into the body, the altered cells lack functional receptors for the virus, reducing the effects of HIV and allowing some patients to interrupt their antiretroviral treatment of the infection. Urnov also observed that the U.S. Food and Drug Administration has approved an application to conduct in vivo early clinical trials using zinc finger nucleases to treat hemophilia B. Other possible targets of somatic cell gene editing mentioned at the summit were sickle cell anemia, thalassemia and other blood disorders, hepatitis and other infections, immune deficiencies, infertility, and cancer. "Genome editing has expanded the definition of the term 'druggable target,'" Urnov said. "If it's in the DNA, it's a druggable target."

"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…we need to combine the knowledge of the natural sciences, the insight of the social sciences and the wisdom on the humanities."

Ismail Serageldin,
The Library of Alexandria

The second category of human gene editing would involve changing DNA sequences in human germ cells, which include sperm cells, egg cells, and the progenitors of those cells. Germline gene editing also could be done in the fertilized egg, in early embryos or later in embryonic development, or in somatic cells that then are induced to become germline cells. With somatic cell gene editing, the altered cells die with each individual patient and do not appear in future generations. Gene editing of germline cells produces changes in DNA that can be inherited by subsequent generations.

Summit participants discussed many possible applications of germline gene editing. Germline gene editing could be used to change genes that cause diseases when inherited from one or both parents, such as the genes responsible for cystic fibrosis, sickle cell anemia, or Huntington's disease. Genes could be altered to protect against diseases -- for example, through modification of the CCR5 gene or of genes involved in heart disease. It could be used to change genetic variants that cause infertility. Germline gene editing also could be aimed at enhancing human traits if genes can be identified and modified to produce desired attributes. Examples mentioned at the summit include enhancing tolerance to particular foods or environments, arresting the cognitive decline or muscle wasting associated with aging, increasing longevity, or altering mental attributes. The ultimate result of germline gene editing could be permanent and substantial changes in the human gene pool.

Many objectives for treating diseases and enhancing human traits could be achieved through somatic cell gene editing. Both Urnov and Rudolf Jaenisch (Massachusetts Institute of Technology) observed that blood and liver cells could be manipulated to produce beneficial proteins, for example, without altering germ cells. Also, parents who want to make choices about the genetic inheritance of their children have options other than gene editing. In preimplantation genetic diagnosis, a cell is removed from an early

Photo of meeting participants left to right: Jennifer Doudna, Bill Skarnes, Feng Zhang, J. Keith Joung, Jonathan Weissman, Jin-Soo Kim, Emmanuelle Carpenter, and maria Jasin.
Source: Pam Risdom

embryo produced through in vitro fertilization and tested for the presence or absence of a genetic disorder, with only those embryos that lack the disorder being used to establish a pregnancy. Other possibilities mentioned at the summit include genetic counseling between prospective partners, the use of sperm or egg donors, prenatal diagnosis and termination of a pregnancy, and adoption.

Many genetic diseases are not amenable to germ cell gene editing, including those caused by new mutations or chromosomal aneuploidies in germline cells, said Peter Braude (King's College London). For the common diseases that have genetic components, such as heart disease, cancer, and many mental disorders, many genes contribute to the disease, and the expression of these genes is often related to a particular individual's environment and experiences. The same observations apply to the genes that shape physical and mental traits in humans, though, as George Church (Harvard Medical School) observed, it is possible to affect some complex diseases and traits through changes in single genes. Genes, however, typically have more than one function, so changing a gene to achieve a desired effect might also have negative consequences. For example, Eric Lander (The Broad Institute of Harvard and MIT) observed that changes to the CCR5 gene can lower a person's risk of being infected by HIV, but altering the gene would also dramatically increase a person's susceptibility to a fatal case of West Nile disease. All humans carry some genetic variants that could cause harm in offspring, and altering all of these variants would be impossible. Furthermore, much about the functioning of genes remains unknown. "Human genetic disease is complex; we still have a lot to learn," said Lander. "Before we make permanent changes to the human gene pool, we should exercise considerable caution."

Patients with genetic diseases have a strong drive to find cures for those diseases, noted George Daley (Boston Children's Hospital). People should not "underestimate the ardor of individuals who are afflicted by disease," many of whom would be interested in germline gene editing if it were clinically available. In addition, the private sector has strong commercial motivations to develop both treatments for disease and procedures to enhance human traits.

Ethical, Legal, and Social Issues

Informed opinions on desired futures for human gene editing differ widely. John Harris (University of Manchester) observed that no new biomedical technology is perfectly safe, and human sexual reproduction results in genetically based medical problems in a substantial fraction of children. Gene editing will be acceptable when its benefits, both to individuals and to the broader society, exceeds its risks, he said, though the relevant risks and benefits and levels of acceptable risk are today uncertain. In addition, human

gene editing provides a means of evolving "by a process more rational and much quicker than Darwinian evolution," Harris said. "What is clear is that we will at some point have to escape both beyond our fragile planet and beyond our fragile nature. One way to enhance our capacity to do both these things is by improving on human nature."

In contrast, Hille Haker (Loyola University Chicago) proposed a two-year moratorium on the basic research needed to enable germline human gene editing until an international ban on germline gene editing for reproductive purposes can be secured through the United Nations and regional bodies can prepare internationally binding regulations. The goal of society should be "to promote a better life for all, and to ensure that everybody can live a life in dignity and freedom," said Haker. "Can this be achieved by germline gene editing? My view is no." The future risks of gene editing are unpredictable, she observed, which means that the long-term harms may well outweigh the benefits. In addition, researchers and future parents have an obligation to respect the morally relevant status of the human embryo, she said, but germline gene editing does not meet this obligation because it either renders the embryo morally neutral or diminishes it to the status of property or goods.

Marcy Darnovsky (Center for Genetics and Society) was similarly cautionary. "Human germline gene editing, if it were to be implemented, would affect and alter not just future human beings but also alter future human societies, perhaps profoundly so," she said. "It is a radical rupture with past human practices." Sharon Terry (Genetic Alliance) noted that patient advocacy groups are as "heterogeneous as the diseases that they represent." In an informal survey she conducted of advocacy group representatives, views ranged from "hell yes" to "we need to look at this scientifically" to "we need to look at the ethics" to "let's talk about this when the scientists have all the technology straight." She reminded the audience that members of patient communities are fighting hard to eliminate diseases while also working to change physical and social environments so that all people can live productive and fulfilling lives. In this context, Ruha Benjamin (Princeton University) pointed out that the line between diversity and disability is fuzzy, and that biomedical researchers can overlook and thereby reinforce stigma and social disparity by treating certain conditions as disabilities that need to be "fixed" through biomedical interventions.

Benjamin and Françoise Baylis (Dalhousie University) also discussed the potential for human gene editing to exacerbate existing inequalities in society. "The use of gene editing techniques is seeded with values and interests, economic as well as social, that without careful examination could easily reproduce existing hierarchies," Benjamin said. As Baylis pointed out, considerations of social justice demand that discrimination and oppression be addressed in preventing disease and promoting health. Similarly, Catherine Bliss noted that well-meaning science that intends to produce benefits for society can unintentionally reproduce social injustices -- for example, in the way that genomics has inadvertently reinforced certain racial categories. Benjamin and Bliss both noted the importance of including diverse perspectives so that assessments of risks and benefits are not limited to medical risks alone.

The prospect of human gene editing inevitably recalls past abuses of human rights involving the biological sciences, and especially the history of eugenics in the first half of the 20th century. As Daniel Kevles (New York University) said, eugenics was not a marginal ideology but "enjoyed the trappings of high professional authority and respectable publicity" in the United States and other countries, being embraced by physicians, mental health professionals, and scientists, including biologists. Eugenics posited that unfit human traits known by such terms as criminality, feeble-mindedness, and pauperism were inherited genetically in the same way as physical characteristics. At the time, eugenic ideas led to widespread forced sterilization and immigration restrictions for individuals and groups thought to be genetically inferior. Only when the Nazis took eugenic ideas to horrific extremes was the concept thoroughly discredited.

Though eugenics is no longer a powerful movement, "several of the forces that animated the eugenics movement a century ago remain vital," noted Kevles. Economic forces to reduce health care costs could put pressure on people to change genetic sequences associated with disease. The association of racial, ethnic, and other groups with particular diseases could lead to new forms of stigmatization. The belief that genes influence particular behaviors or other complex traits could lead to pressures to change those genes in future generations. And consumer demand for particular attributes in offspring could lead people to pursue private sector options for human gene editing that are difficult to regulate.

The Governance of Human Gene Editing

The governance of human gene editing can draw on a wide variety of institutions, policies, and practices. Governance involves not only governments but private industry, research and educational institutions, advocacy organizations, and professional societies. It encompasses such issues as intellectual property rights, trade laws, regulatory frameworks, cultural attitudes, and

public research investments. Governance can be exerted through laws, regulations, guidelines, standards, professional norms, and public expectations.

As Alta Charo (University of Wisconsin, Madison) pointed out, major aspects of governance can differ among countries. Overall approaches can range from promotional to permissive to precautionary to preventive, with differences in regulatory and legislative restrictions, government guidelines, voluntary self-regulation, and public consultation. A panel of representatives from Nigeria, Germany, France, Israel, South Africa, Sweden, and India highlighted the many ways in which policies toward genetically engineered foods, human clinical therapies, stem cell research, and assisted reproductive technologies vary among nations. They also observed that the needs of countries vary dramatically. For example, Nigeria is very interested in human gene editing, given that it has the highest number of sickle cell cases in the world, observed Fola Esan (Nigerian Academy of Science), but the country would need to improve its clinical and research capacity to take advantage of the technology. Israel, in contrast, offers its citizens extensive support for prenatal genetic interventions such as preimplantation genetic diagnosis, in part because Jewish religious authorities have a generally favorable view of research that leads to therapeutic benefit, said Ephrat Levy-Lahad (Shaare Zedek Medical Center and Hebrew University Medical Center).

However, each of the seven panelists, along with other speakers at the summit, noted that their countries have in place provisions that act to prohibit germline gene editing. For example, Zhihong Xu (Peking University) said that, in China, "the manipulation of the genes of human gametes, zygotes, or embryos for the purpose of reproduction [is] prohibited." Bärbel Friedrich (Leopoldina – The German National Academy of Sciences) noted, "the German Embryo Protection Act prohibits artificial alterations of genetic information of a human germline and the use of a human germ cell with artificially altered genetic information for fertilization."

Photo of meeting participants left to right: George Daley, Jennifer Doudna, and David Baltimore
Source: Pam Risdom

Indira Nath (All India Institute of Medical Sciences) commented that governance is becoming increasingly international and participatory, especially given the role that the public now plays in shaping policies. "It's no longer possible to control technologies by the laws of one country," she said. "If there is a demand for a technology, people will go to whichever country has it."

"Governance regarding technologies is now crossing geographical borders, and with national policies becoming rapidly transnational, one would say that governance is no longer just local, but is becoming a network of nations working together."

Indira Nath, All India Institute of Medical Sciences

Treaties and other formal international agreements require large commitments of resources, time, and political capital and often pose enforcement challenges. Given these difficulties, international governance is moving from hard law marked by enforceable requirements to "soft law" that provides expectations that are not enforceable but are implemented through other mechanisms on a more voluntary basis, said Gary Marchant (Arizona State University). These new governance arrangements broaden oversight from top-down government regulators to include a much wider range of decision makers, including companies, researchers, nongovernmental organizations, public-private partnerships, and other parties.

An extension of this approach, at both the national and international levels, is what Thomas Reiss (Fraunhofer Institute for Systems and Innovation Research) termed "responsibilization," where societal stakeholders and innovators share mutual responsibility for the impacts, consequences, sustainability, and acceptance of innovation. Responsibilization goes beyond initiating a public debate or engaging with stakeholders, he said. By abolishing the separation of science and technology from public discussion and governance, it represents a fundamental transformation of the innovation system. "It could lead to a shared responsibility of all relevant stakeholders on the key issues and on the governance of human gene editing," Reiss said.

One aspect of responsibilization is acting to prevent irresponsible or malicious uses of gene editing technologies. As David Relman (Stanford University) observed, the research community needs to sensitize "our communities of colleagues, [and] all stakeholders, so that there is at least a chance of recognizing something that has gone amiss at an early stage and preempting it."

The range of stakeholders for human gene editing is very broad, observed Charis Thompson (University of California, Berkeley). People whose voices need to be heard include public interest advocates in the fields of disability rights, racial justice, women's health, reproductive rights and justice, the LGBT community, environmental protection, and labor, as well as members of the general public, since everyone has a stake in this issue, she said. Furthermore, groups and individuals, including those with religious perspectives, can be expected to have a wide range of attitudes toward human gene editing, which means that broadly based discussions will be needed to reach widely shared agreements.

Statement from the Organizing Committee

In the final session of the summit, the 12-member organizing committee released a statement that summarized its conclusions from the meeting, and the Presidents of the four sponsoring Academies responded to the statement. (The statements are included below.) An inclusive, ongoing global conversation will be essential, both statements said, to assess the many scientific, ethical, and social issues associated with human gene editing. "This summit will not be the last word on human gene editing," concluded organizing committee chair David Baltimore. "Rather, we hope that our discussion here will serve as a foundation for a meaningful and ongoing global dialogue."

"...process and policy have to go hand in hand. We jump to thinking about what kind of policies we want, assuming that we have a solid understanding of what process is going to get us there. ...we really need to think carefully about whose around the table, whose expertise is valued."

Ruha Benjamin, Princeton University

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.

Statement by

Ralph J. Cicerone, President, U.S. National Academy of Sciences
Victor J. Dzau, President, U.S. National Academy of Medicine
Chunli Bai, President, Chinese Academy of Sciences
Venki Ramakrishnan, President, The Royal Society

We thank the organizers of our International Summit on Human Gene Editing for their thoughtful concluding statement and welcome their call for us to continue to lead a global discussion on issues related to human gene editing. Together with academies around the world, and in coordination with other international scientific and medical institutions, we stand ready to establish a continuing forum for assessment of the many scientific, medical, and ethical questions surrounding the pursuit of human gene-editing applications. The forum will mobilize the global expertise necessary to help society develop norms for acceptable uses of human gene-editing technology. This is an important moment in human history and we have a responsibility to provide all sections of society with an informed basis for making decisions about this technology, especially for uses that would affect generations to come.

We also want to thank the organizing committee for bringing together so many renowned experts, from many parts of the world and from a variety of disciplines, who for the last three days engaged in such insightful discussions about advances in human gene-editing technologies and their implications for research, medicine, and society.

Organizing Committee for the International Summit on Human Gene Editing: David Baltimore (chair), California Institute of Technology; Françoise Baylis, Dalhousie University; Paul Berg, Stanford University School of Medicine; George Q. Daley, Boston Children's Hospital and Dana-Farber Cancer Institute; Jennifer A. Doudna, University of California, Berkeley; Eric S. Lander, Broad Institute of Harvard and MIT; Robin Lovell-Badge, The Francis Crick Institute; Pilar Ossorio, University of Wisconsin; Duanqing Pei, Guangzhou Institutes of Biomedicine and Health, Chinese Academy of Sciences; Adrian Thrasher, University College London Institute of Child Health; Ernst-Ludwig Winnacker, Ludwig-Maximilians University of Munich; Qi Zhou, Institute of Zoology, Chinese Academy of Sciences; Staff: Anne-Marie Mazza, Project Director; Steven Kendall, Program Officer; and Karolina Konarzewska, Program Coordinator.

This meeting in brief has been prepared by Steven Olson as a factual summary of what occurred at the Summit. The statements made are those of the author or individual meeting participants and do not necessarily represent the views of all meeting participants, the U.S. National Academy of Sciences, the U.S. National Academy of Medicine, the Royal Society, or the Chinese Academy of Sciences.

The summary was reviewed in draft form by Dana Carroll, University of Utah; Benjamin Hurlbut, Arizona State University; and Steven Joffe, University of Pennsylvania, to ensure that it meets institutional standards for quality and objectivity. The review comments and draft manuscript remain confidential to protect the integrity of the process.

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