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Gene editing
in an international context:
Scientific, economic and
social issues across sectors

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Note by the BNCT Secretariat

This workshop report has been kindly provided by the BNCT Delegation of Canada, which hosted the workshop on “Gene editing in an international context: scientific, economic and social issues across sectors”, held on 29-30 September 2016 in Ottawa, Canada.

This report aims to capture the opinions expressed by invited experts during the meeting, and reflect the discussion during the application-specific breakout groups and plenary sessions held at the meeting. This report does not represent the views of the OECD Working Party on Biotechnology, Nanotechnology and Converging Technologies (BNCT) or those of its delegates.

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Executive Summary

Gene editing techniques are a major advance that could have major benefits across the domains of human health, sustainability and the economy that go beyond incremental advances of past biotechnologies. In the context of agriculture and aquaculture, the potential benefits include opportunities for improved efficiency, greater productivity, broader varietal repertoires. In human medicine, gene editing technologies might lead to new cures and therapies for genetic diseases, controls for vector-borne diseases, and improved vaccines. Environmental applications of gene editing technologies could enable novel approaches to conservation, bioremediation, the control of invasive species, and the protection of biodiversity. These issues were addressed at a Workshop held in Ottawa, Canada, on September 29-30, 2016.

There are significant policy challenges at the national and international level related to the governance of gene editing. Some of these issues do not differ significantly from those arising from older genetic modification techniques/technologies. But it was agreed among workshop participants that some issues are unique to gene editing given the wide range of potential applications across sectors and the increasing precision, efficiency and accessibility of gene editing technologies. General points about governance include the need to earn and foster public trust in regulatory institutions, to cure high regulatory uncertainty, and to set regulatory measures at a reasonable level.

At least in some of the areas of application, existing regulatory frameworks are under fresh scrutiny. Experts attending the BNCT workshop were concerned that existing approaches might be too restrictive. There is also some agreement, but not across all application areas, that conventional risk analysis frameworks may need to be adjusted or enlarged, in order to face challenges and new questions presented by gene editing technologies and to alleviate public concerns. Within any framework, potential benefits should not be neglected in the analysis; furthermore, given that negative results cannot be proven, improbable theoretical risks should be balanced against quantifiable risks of inaction. Governments and policy makers were urged by workshop participants to consider the applications and their consequences on a case-by-case basis, if necessary, in order to facilitate timely decision-making.

The issues surrounding the intellectual property protection of gene editing technologies are manifold. First, a growing number of patents and patent applications cover or involve gene editing technologies. This development deserves further observation, in order to identify any adverse effects on innovation in the future. Second, the settlement of ongoing litigation on key patents would increase certainty for the already large and fast growing number of licensees and laboratories employing gene editing technologies. Third, IP rights involving gene editing technologies can contribute to a legal framework that provides for access to such widely applicable technologies, on one hand, while promoting responsible use on the other.

Some of the questions raised and discussed at the workshop may have wide-ranging ethical implications. The underlying perception was that some applications of gene

editing may be a catalyst to ask fundamental questions, such as where the human species is heading. Most workshop participants agreed that engaging publics early about gene editing and its potential uses would be crucial for shaping and promoting technological diffusion. Although gene editing technologies are still in their infancy, the scientific community has already made efforts to engage various publics through diverse media vehicles; such efforts should be encouraged.

1. Introduction

New and emerging gene editing technologies have resulted in many new and important policy questions regarding our environment, our health and our economies. Governments, policymakers, and scientific communities from across the globe are actively exploring ways to address the impacts of these new technologies from economic, legal and social perspectives. In support of this effort, the OECD Working Party on Biotechnology, Nanotechnology and Converging Technologies (BNCT), in collaboration with the Canadian Government held an international meeting entitled, “Gene Editing in an International Context: Scientific, Economic and Social Issues across Sectors”. The workshop agenda can be found in Annex A.

Held in Ottawa, Canada, on the 29-30 September 2016, the workshop brought together government officials and international organisations, as well as invited experts from 15 countries. A list of invited experts can be found in Annex B. The meeting was designed to examine the application and impacts of gene editing across a variety of sectors, but focused primarily on applications for environmental management, human medicine, agriculture and aquaculture.

Background material distributed prior to the workshop was used to inform participants and provide context to sectoral discussions. Presentations during the three break-out sessions addressed gene editing governance, applications and sector-specific issues. Organisers of each breakout group received identical questions and instructions so that common issues could be identified along with sector specific issues.

The workshop had been conceptualised to inspire broad discussions among scientists, business leaders, policy makers, opinion leaders and government representatives. It crossed disciplines and national boundaries to facilitate the exchange of knowledge and featured three smaller expert discussion sessions on (a) human medicine, (b) agriculture and aquaculture and (c) the environment, respectively. The issues and ideas raised in this report do not reflect any single or collective jurisdiction, government, or institution; the ideas that are summarised herein are points to consider as decision-makers consider gene editing technologies and their applications.

2. What is gene editing?

In general, gene editing refers to a set of novel techniques for manipulating the genome that can achieve much greater precision than pre-existing forms of genetic engineering. The best known and most consequential of these techniques is the so-called CRISPR-Cas9.¹ Gene editing technologies are to have major implications for innovation across biomedicine, agriculture, and industrial biotechnology because genetic manipulation is now more exact, less expensive, and easier. Gene editing tools are already regarded as extremely valuable contributions to biotechnology and molecular biology.

Gene editing techniques have been around for a long time. It is the advent of CRISPR/Cas9, however, that has propelled the field forward, reducing costs and making techniques easier and more available. Unless stated otherwise, in this report, the term “gene editing” refers to the use of site-specific nucleases, such as CRISPR/Cas9, TALEN or ZFNs, to insert, delete, or alter either one or more DNA nucleotides.^{2,3} This type of editing - not to be confused with other forms of gene editing such as RNA splicing - can be used to target a single specific site, or several at once. The effect is a homologous editing of an organism’s genome that can target either coding or non-coding regions to achieve a range of results. The precision and speed of gene editing enables a wide range of beneficial applications – including treating genetic diseases, global food security and environmental remediation.

3. Unravelling hope and hype

Much of the public discourse surrounding gene editing has focused on its potential promise for addressing complex and interrelated societal challenges. Nevertheless, like with many emerging and disruptive technologies before it, some scepticism exists about whether gene editing technologies will live up to their potential and can be practically deployed to address societal and industrial challenges. While gene editing is already being deployed in clinical trials and commercial applications, it remains to be seen whether it is simply the latest gadget in the biotechnology toolbox, a revolutionary disruptor of fundamental research and development, or something else altogether.

From time to time scientific breakthroughs offer great promise, which are expounded upon and amplified in the media, but then may which fail to deliver on their promise. Gene editing seems set to be different and appears to truly represent a significant leap in the capability of mankind. However, to deliver on its promise, it is important to understand the context of gene editing and what is required to enable the responsible development of the technology.

For some time, science has needed RNA-guided site-specific nuclease-directed gene editing technologies, such as the most widely used CRISPR-based techniques, to enable a new series of scientific breakthroughs. Gene editing represents a suite of affordable, accessible, flexible, easy-to-use tools that can yield quick results. Not since the PCR (polymerase chain reaction) tool has there been such wide uptake by bench and clinical scientists. The most widely used gene editing platforms:

- need only a small investment
- can be applied easily to a range of experiments
- work with existing experimental techniques
- deliver results in far shorter times than other techniques, such as selective breeding or mutagenesis.

The wide and diverse range of possible gene editing applications in human medicine, agriculture, aquaculture and the environment have positioned the technology as a possible means to develop novel solutions for addressing challenges on the global scale, as well as those at the national and subnational level. For instance, gene editing technologies have the potential to:

- develop treatments for incurable genetic disease
- increase food production
- increase energy production
- reduce invasive species
- remediate or replenish certain natural resources
- increase genetic variation in domesticated species.

Moreover, while the inherent power of gene editing technologies has created new capabilities to alter living organisms beyond what was ever possible before, so too does it

hold the potential to create unintended disruptive effects, perhaps even with vast consequences to the living ecosystem. Even if it was assumed that expert communities and governments will eventually possess the capacity to sufficiently model the impact of gene editing applications, there is still uncertainty if they can/should be used, and by whom and in what context. Consequently, a first step towards addressing the technical, philosophical and ethical issues associated with gene editing applications will be to understand the fluid landscape, in which decisions have been, are being, and could be made.

“The world is in crisis. Gene editing is not the total solution, but it is an important part of the solution.” (Perry Hackett, University of Minnesota / Recombinetics, USA)

4. Potential benefits

Gene editing opens possibilities that were once unforeseeable or hard to realise practically. Never before has a technology so precise, quick, and inexpensive been available to alter the DNA of any species – including our own. Its benefits converge with and go beyond the incremental advances of past technologies. Presentations and workshop discussion of the potential benefits of gene editing are listed below with examples.

4.1. Applications in agriculture and aquaculture

The potential benefits of gene editing in the agriculture, aquaculture and bioeconomy sectors can be broadly categorised as improved efficiency and greater productivity. The potential reduction in animal suffering has also been cited. Some specific examples that were identified by participants are listed in Figure 4.1 below.

Figure 4.1. Gene editing benefits for agriculture, aquaculture and the Bioeconomy

Note: Excerpt from the slide show used to report from the workshop breakout session to the plenary session.

Source: Slide show created by the breakout group on applications in agriculture and aquaculture, Ottawa, September 2016.

Improved efficiency

Pierre-Benoit Joly (French Institute for Research and Innovation in Society and French National Institute for Agricultural Research, France) cautioned that a central question for gene editing applications in agriculture was whether they will actually prove more efficient than genomic selection. To realise the promise of efficient, gene editing should build on complementary advances in genomics, synthetic biology, metabolic engineering, genomic selection, traditional plant breeding and animal selection. Such complementary, and even converging advances could further drive down the cost of use.

One of two key-note speakers, Perry Hackett (University of Minnesota / Recombinetics, USA) spoke about using gene editing to breed a dairy cow variety without horns, called a “polled” breed. Most Dairy breeds were born with horns, which were removed mechanically from calves – a painful process. In contrast, some beef cattle were polled as a result of years of breeding. Gene editing could produce, in a single generation, one animal bearing both polled and dairy merits, a result Hackett estimated, that would otherwise take 25 to 30 years of intense backcrossing of dairy and beef breeds.

At the University of Minnesota in November 2015, two male dairy cows were born, which were homozygous for the polled allele. Genome sequencing with a 20-fold coverage found no off-target effects.⁴

Greg Gocal (Cibus, USA) described a process to generate single nucleotide changes in plants using gene repair oligonucleotide (GRON) and the host plant’s enzymes. He gave the example of editing, in flax, the EPSPS gene, an enzyme used in aromatic amino acid metabolism pathways (Sauer et al., 2016^[1]). He noted that these gene editing experiments showed no unintended or off-target effects, and succeeded in regenerating a whole plant from a single edited cell.

Invited expert Seiichi Toki (National Agriculture and Food Research Organisation, Japan) and his colleagues explained how they have used gene editing technology since 2010 to target mutagenesis in Arabidopsis and have developed a method to edit rice at an efficiency rate of 80% into rice. The CRISPR/Cas9 system could be used to target multiple genes and stack agronomically important traits in rice and other species.

Greater productivity

Gene editing in agriculture is not limited to introducing agronomically important traits. The invited expert Francois Eudes (Agriculture and Agri-Food Canada, Canada) noted that perennial cereal crops showed that the benefits can also include greater productivity through reduced labour and other farming costs, deep root systems that reduce greenhouse gas emissions, increased carbon capture and reduced nutrient loss. Past attempts to develop perennial cereal crops had failed, because of genomic instability and genetic conflicts between annual and perennial parental strains. Advances in gene editing could make these crops a reality.

Greg Gocal spoke from a biotechnology industry perspective, saying the convergence of genomics, gene editing and cell culture techniques had enabled a new non-transgenic technology industry, especially in agriculture. This included reintroducing crop diversity that had been lost through intensive breeding, with the aim of bringing back beneficial traits found in wild relatives of domestic crops.

Simon Lillico (The Roslin Institute and R(D)SVS, UK) spoke about the great diversity among domesticated breeds of cattle, sheep and pigs. Variations in domestic breeds

resulted from classical breeding and selection techniques, but selective breeding was time and resource intensive, and gene editing technology could make it more efficient. Lillico suggested using genotype and phenotype data from select populations to develop algorithms that predicted breeding merits. Breeders could then use gene editing to make specific modifications based on the genetic variations that caused these merits to restore the loss of diversity caused by traditional breeding.

The invited expert Anna Wargelius (Institute of Marine Research, Norway) presented research underway in Norway using gene editing on Atlantic salmon, a species chosen for research because of its great potential to feed the world's population. However, there were concerns over sustainability, impacts on wild populations and sustainable feed resources. Wargelius used gene editing to increase the speed of salmon growth, coupled with a gene drive system, as one possible application of gene editing approaches, to produce sterile cultured fish, to contain cross breeding with wild types. While sterility might appear desirable from this perspective, there had been highly reactive and vocal public rejection when Genetic Use Restriction Technology was proposed for plants – the often dubbed “terminator technology”. Wargelius proposed that if reliable genetic sterilisation could be accomplished with gene editing, knockdown technology or triploidisation, then gene editing could also be used to re-introduce natural wild genetic variation into cultured salmon.

In salmon, gene editing could be used to modify fatty acid metabolism, improve disease resistance (as with controlling salmon lice, ion balance and reproduction). Editing these traits within a frame of natural variations could reduce risk and ethical considerations, compared to transgenic approaches.

Francois Eudes described how the International Wheat Improvement Network and Agriculture and Agri-Food Canada used gene editing to produce agronomically important traits such as drought tolerance, heat resistance, high yields, erucic acid-free oil, glucosinolate-free canola and dwarf rice. Notably, unintended genetic changes observed in gene edited plants fell within the range seen using classical methods.

David Zilberman (University of California Berkeley, USA) reminded the workshop of a key fact underpinning gene editing for agriculture: hybrid crops and livestock breeds used globally today already differ significantly from their wild ancestors.

4.2. Applications in human medicine - general

The benefits of gene editing in human applications can be roughly separated into “germline” and “somatic” applications. Gary Marchant (Arizona State University, USA) said that the pursuit of applications in somatic cells to address disease was widespread, and that there was broad agreement that germline editing of human cells for reproductive purposes was considered unethical.⁵

Potential benefits to human health were described by several presenters; the main benefits are detailed below. Additional benefits that were raised throughout the workshop are listed in Figure 4.2 below.

Figure 4.2. Potential benefits of gene editing for human health and nutrition

Note: Excerpt from the slide show used to report from the workshop breakout session to the plenary session.

Source: Slide show created by the breakout group on applications in human medicine, Ottawa, September 2016.

4.3. Applications in human medicine - malaria

The invited expert Nicole Achee (University of Notre Dame, USA) explored policy issues around gene drive technology for vector control; she introduced a hypothetical case study of reducing malaria on Sumba Island, Indonesia. The idea was that gene editing might be used to remove mosquitoes’ parasite and insecticide resistance, in order to eradicate malaria. The mosquitoes had been generated in proof-of-concept studies, but optimisation experiments remain underway to ensure no off-target events and refine targeting of mosquito mating locations on Sumba Island. The policy issues around gene drives research and innovation were recently explored in a U.S. National Academy study (National Academies of Sciences, Engineering, 2016^[2]).

Data released since the workshop shows that mosquitoes can develop resistance to gene drives (Callaway, 2017^[3]). Some evidence also suggests that wild mosquitoes may propagate gene drive resistant genes instead of the engineered mutations. In addition, genetic analysis of African mosquito species found significant variations, suggesting that selecting a suitable gene drive target may be more difficult than originally thought. Multiplexing targets in a gene or throughout the genome of *Anopheles* may hold an answer. Research outcomes of Target Malaria’s experimentation will supply additional insight.

4.4. Applications in human medicine - understanding of fundamental biology

Fredrik Lanner (Karolinska University, Sweden) described how gene editing could increase the understanding of fundamental and developmental biology. Editing genes expressed during the first week of human development, before implantation and formation of the primitive streak, were key to understanding causes of infertility. Researchers had used mice to model human embryonic development, but the advancement of understanding over the last 20 years had been limited by key differences

between the molecular mechanisms and the genetics that govern the early development in mice and in humans.

Lanner's research was aimed at profiling genes expressed from day to day for each individual cell that forms a human embryo during the first week, or until a blastocyst forms. He did this by disrupting one gene at a time to observe how it developed through several cell divisions. The blastocyst had three distinct cell types: trophoblast cells, which developed into the placenta; primitive endoderm cells, which became the yolk sac, and embryonic cells. The research into the fates of each of these cell types and individual cells, in particular, seemed likely to answer a key question in developmental biology, such as when specific cell types emerged?

4.5. Applications in human medicine - xenotransplantation

Globally, there is a shortage of organ donors. Xenotransplantation could be used to supply organs from animals, and pigs have frequently stood in for humans in medical research. The invited expert Rolf Zeller (University of Basel, Switzerland) cited research by George Church that removed a porcine endogenous retrovirus from a pig genome, as a major step toward achieving xenotransplantation (Yang et al., 2015^[4]). The history of using animal organs in human medicine is filled with technical and ethical challenges, but this development may hold a way to reduce human rejection of animal organs. Alternatively, gene editing could also be used to engineer "humanised" animal organs to avoid host rejection.

4.6. Applications in human medicine – therapeutic applications

Any list of possible therapeutic applications for gene editing technologies proposed at the time of the workshop will be outdated when this report is published. It is difficult to keep pace with developments and discoveries in the areas of gene editing and disease aetiology or therapeutic intervention. Targeting monogenic diseases such as Duchenne muscular dystrophy or cancer through drug discovery are common targets of gene editing researchers (Ousterout et al., 2015^[5]; Shen et al., 2017^[6]; Wojtal et al., 2016^[7]).

Krishanu Saha (University of Wisconsin-Madison, USA) spoke about using gene editing to modify proteins that play a role in adverse reactions to therapeutic treatments, including cell therapy and transplants. His research and experience led him to say that reaping the potential human health benefits from gene editing would take regular conversations between researchers and engineers.

4.7. Environmental applications

Several presentations and discussions focussed on the applications of gene editing in agriculture and human medicine, but environmental impacts and applications were mentioned throughout the meeting; as such, it was noted that biomining could reduce conventional mining's environmental impacts by using edited microbes to extract and concentrate minerals. Gene edited microbes could also be used in bioremediation, for example to degrade contaminants such as oil spills. Specific examples of environmentally relevant applications are discussed below. Additional benefits were raised throughout the workshop and are summarised in Figure 4.3 below.

Figure 4.3. Gene editing benefits for the environment and the ecology

Note: Excerpt from the slide show used to report from the workshop breakout session to the plenary session.

Source: Slide show created by the breakout group on environmental applications, Ottawa, September 2016.

Gene drives could limit the spreading of invasive species and thereby improve conservation efforts, said Mark Tizard (Commonwealth Scientific and Industrial Research Organisation, Australia), illustrating the concept on the example of cane toads in Australia: cane toads were not only an invasive species, but could kill the indigenous wildlife that normally served as predators. Tizard said Australian researchers hoped to use gene drive to decrease the cane toad population by introducing genetic changes that reduced the amount of toxin the toads produce, thereby making it part of the indigenous food chain.

With gene drives, Kevin Esvelt (Massachusetts Institute of Technology, USA) saw tremendous potential for good, including reducing or eradicating vector-borne diseases and continent-scale invasive species. Esvelt said he saw few reasonable applications for global gene drives. His work clarified his views on gene drive-specific considerations:

- Contained field trials are risky, because it would take only one person to deliberately move an organism from one climate to another to unleash a global spread.
- Local drives are advantageous, because they could spread quickly, were transient and could remain local. Introducing self-limiting traits was costly, but there were applications that could be justified, such as eradicating the Australian cane toad. Local gene drives gave control to the local communities.
- Experts acting alone would not be able to fully identify or weigh the true costs and benefits of gene drives.

5. Risks

As with any new technology and its potential applications, the risks and uncertainties of gene editing are not fully apparent at the outset. Workshop participants identified many risks that were common across sectors, while other publications have identified even more. Some possible risks may simply be uncertainties that could be addressed as the field advances; others may call for more thought about the roles of ethics and governance and more public engagement.

Figure 5.1 summarises the issues raised during the workshop as being relevant, although not necessarily unique, to gene editing applications across the different sectors.

Figure 5.1. General issues across sectors raised by workshop participants

Source: Canadian Delegation to the BNCT, April 2017.

5.1. The potential perils of inaction

The global community has to consider that some nations, like some individuals, may be more comfortable with, or may need or want to accept higher levels of uncertainty about potential risks than others. Moving forward, it will be important to describe the potential risks and uncertainties in detailed and nuanced ways so that decision-makers can make their decisions.

Workshop participants were careful to balance the potential for gene editing applications to tackle global grand challenges against potential risks arising from innovating for the sake of innovation and from misuse. These potential risks may overshadow potential benefits in the absence of fully developed and fit-for-purpose mechanisms for governance and oversight. However, there was broad consensus among workshop participants of the pitfalls that could also come from doing nothing at all.

Workshop participants discussed, at length, the need to balance regulatory costs against the risk of not using gene editing technology to address grand challenges. The possibility of accidents may stall experimentation and commercialisation, but development would nevertheless continue. Some workshop participants noted that there was further need to develop more robust applications and give decision makers and the public more time to consider impacts and how to use and govern the technology.

Governments assessing the comparative risks of the various delivery mechanisms, gene editing machinery and guided RNAs may benefit from sharing information and frameworks regardless of how they choose to regulate. As scientists refine gene editing systems, governments that must assess the comparative risks of different gene editing technologies stand to gain from sharing information. How patents affect open knowledge about critical parts of gene editing systems will also be an area of international interest.

5.2. Public engagement

Throughout the workshop and across all sectoral tracks, some participants and discussion leaders noted the need for early and ongoing public engagement on the use of gene editing technologies. To date, media coverage of gene editing has been relatively balanced in comparison to genetic manipulation technologies that have come before it and has led to more sophisticated responses from the public than some past technologies. Some workshop participants urged harnessing this so-far-positive momentum to speak to gene editing's risks and benefits, to increase exposure, and to create opportunities for iterative discussion and knowledge exchange. The benefits of public engagement are illustrated in Figure 5.2 below.

Participants and presenters gave examples to illustrate the importance and purposes of meaningful public engagement.

Perry Hackett likened gene editing to mobile phones, in order to illustrate how focusing on uses rather than the technology itself could help to inform better discussions about gene editing. The analogy, he said, was that for users looking for its advantages, gene editing's rapid operation and personalisation were key features. Like with mobile phones and other disruptive technologies, the risk of misuse, when positioned against the potential benefits of specific applications, could benefit from discussing and deciding upon appropriate restrictions and controls.

Figure 5.2. Good practices for public engagement

Findings from the international workshop

Source: Canadian Delegation to the BNCT, April 2017.

Hackett's illustration points to a key element of public engagement: making it meaningful.

Participants noted that, in order to not make the public feel overwhelmed or afraid in trying to understand gene editing, the focus of meaningful public engagement efforts should be on the advantages of specific applications and products rather than on the technology itself.

Meaningful public engagement was seen as particularly challenging for specialised communities such as scientists and governments seeking to ensure that information was offered and received respectfully and appropriately. At the same time, public engagement on gene editing was understood as being an opportunity to educate and advocate for evidence-based decision-making. Some participants agreed that meaningful public engagement necessitated the clarifying of differences between the hype and hope of gene editing, while also ensuring that individuals and groups could raise issues, air dissent and work towards solutions.

Approaches to public engagement

Workshop discussions of the examples detailed below focussed on several common features of effective dialogues with publics, including:

- early, continuous and transparent
- inclusive
- culturally sensitive
- designed to build and maintain trust.

Early, continuous and transparent

There was a common view among participants that given that this technology would not pause for deliberations, engaging the public on gene editing was most meaningful when it could be iterative and feature continuous, transparent multilateral communication. The

rapid pace of development and increasing social media presence created an environment ripe for continuous engagement that could be used to deliver appropriate information, hear concerns and conduct research using the most current information.

The invited expert Delphine Thizy's (Imperial College London, UK) presented a stakeholder engagement strategy for Target Malaria's use of gene drives to suppress *Anopheles gambiae* mosquitoes and so reduce malaria's spread in Africa that started with the regulatory sector: the strategy focused on the co-development of the technology with regulators by engaging early – before the technology was ready for deployment. This early engagement allowed regulators to identify the regulatory obstacles and seek early public engagement. A key feature of this strategy had focussed on communicating the features of gene editing rather than its process, which allowed regulators to consider different regulations for different applications. The result had been co-development and integration of ideas into an approach to deployment, rather than simply informing those affected. Given that genetically engineered mosquitoes were borderless, the goals for early engagement were to raise awareness, to identify potential risks and mitigation measures and to inform regulatory oversight.⁶

In 2017, Target Malaria aimed to hold further engagement sessions with regulators in East, Central and Southern African communities. Early engagement ensured that concerns that different publics raise will be integrated into independent risk assessments and into the technology's co-development.

Research by the invited expert Kevin Esvelt into using gene drives to eliminate Lyme disease in the United States included a very early stakeholder engagement stage, a step he specifically recommended for all gene drive research, as well as for the broader scientific community. He said it was important to tell publics what a gene drive may do before pursuing any other financial or time-sensitive goals. The simple, open acknowledgement that (in this instance) gene editing could affect others would increase public trust.

Esvelt emphasised the need for early engagement by challenging the participants: do scientists have a special responsibility? In his opinion, yes, they do: they were morally responsible for whatever they discovered or invented, and there were direct implications for regulation. He further suggested that it was important to tell people what was possible before it was done, and to be open when one's research could affect others.

Esvelt said that openness, collaboration and collective scrutiny were key contributors to biosecurity, biosafety and public confidence. He advocated for open sharing of gene editing proposals before experimentation begins and suggested consultation with communities likely to be impacted.

Ken Oye (Massachusetts Institute of Technology, USA) reinforced this theme by asking the participants to consider the best way to use time before a technology fully matures: scientists, he said, could use this time to assess security and environmental effects and flag uncertainties for direct research and to develop safeguards and codes of conduct. Policy makers, including governments, could use it time to identify gaps and anticipate ways the system might be gamed.

Some workshop participants acknowledged that moving forward, it would be important to deliberately frame discussions within specific contexts while being open to an ongoing reframing as new knowledge was generated. With gene editing, making conscious efforts from the outset to keep conversations and public engagements from being constrained was seen as necessary to upholding the integrity of both the public engagement activities and of the individuals and institutions involved in undertaking this democratic imperative.

On the other hand, there was also broad recognition of the inherent challenge for decision makers and knowledge generators with respect to demonstrating openness in the framing and reframing of discussions, while also ensuring that public engagement efforts were not only inclusive but constructive.

Engagements were crafted to acknowledge evidence that is presented. It was difficult to label public engagement as responsible without all of this information. The question “Who is made responsible for defining the evidence used to understand the technology and its uses?”, was as important a question as “How should public engagements be held?”. Consequently, some workshop participations noted that responsible public engagement required all relevant available evidence to be presented, and encouraged those charged with designing and implementing public engagement strategies and activities to be mindful in determining the relevance of specific evidence and information.

Industry’s approaches to GMOs in the recent past illustrate the challenges associated with engaging the public too late in discussions regarding the technology, its applications and benefits. With this lesson in mind, the need for public engagement on gene editing was seen as an opportunity to learn from the past and seek early, proactive, deliberative and transparent engagement with the public. Participants agreed that gene editing might not be able to deliver on its early promise unless governments, industry and researchers heeded lessons learn from engaging the public on older genetic modification technologies.

Inclusiveness

The implications of plausible gene editing applications are inherently broad and potentially profound. Furthermore, the ways that gene editing applications could affect families, species, continents and ecosystems may not always be direct, obvious or possible to anticipate; for this reason, some participants agreed that a broad cross-section of society should be consulted to ensure that all voices were heard. Globally, the potential for genetic and financial flow makes engagement between nations – especially those sharing borders and trade – a practical necessity.

The key-note speaker Sheila Jasanoff (Harvard University, USA) used the example of scientists and farmers to illustrate that different groups had different understandings: scientists had a different perspective and understanding of animals than farmers. Both were specialised and important. Inclusive public engagements, therefore, benefited from engagement with a broad group of stakeholders to ensure that the opinions and expertise of majority and minority groups were included.

Because inclusion and diversity are vital to democracy, workshop participants were urged to think about ways to capture the voices of those not present at engagements.

Culturally-sensitive recognition of ethics, beliefs, knowledge systems, politics, religion and more

Nicole Achee illustrated the need for public engagement strategies to be culturally sensitive by describing her effort to introduce gene edited mosquitoes to combat malaria in Indonesia. Culturally sensitive public consultations involved processes and formats develop for the particular ethics, beliefs, knowledge, politics, religion and other components of the society or community, in which the technology was being developed and applied. Achee noted that in certain communities, religion, local governance and

customs effective public engagement would depend on who was chosen to deliver the message or conduct the engagement.

Achee added that: while there were similar considerations across different locations and applications for malaria control, solutions would have to fit each context. The Sumba Island case study featured distinct ecologies that included subsistence farming, mountains and arid areas where starvation was a major concern for the population. The hierarchical government included local communities headed by elected chiefs. Religion, local customs and animism could be important considerations for the population. Accounting for all of these elements and issues had been vital to Target Malaria's gene drive research. The detailed approaches to risk-benefit-uncertainty analyses might be different in different places and thus impact decision-making.

Hidenori Akutsu (Cabinet Office, Japan) presented current Japanese tools for engaging in national discussions on gene editing. In Japan at present, advancement of human gene editing is awaited as the breakthrough technique for many medical fields, which were currently without other treatment options, but tied to an understanding that government and academic societies had to set strict rules for application. To this end, expert organisations had convened to discuss and to make recommendations for using gene editing on fertilised embryos. The Japanese Expert Panel on Bioethics, Japanese Society of Gene Therapy, Japanese Society of Human Genetics, Japanese Society of Obstetrics and Gynaecology and the Japanese Society of Reproductive Medicine and the Science Council of Japan were all giving their expert perspectives.

Furthermore, public engagement sessions were also held to inform the Interim Report that the Japanese Expert Panel on Bioethics produced regarding using human gene editing in fertilized embryos. Japan viewed communication with other countries as crucial to the engagement process, because there was an understanding that some applications of gene editing were borderless. Being open with partner jurisdictions and understanding common problems was imperative to the technology's judicious use, especially in humans.

Jasanoff challenged the workshop participants to think about how to frame public engagement: human life could be framed in a material way based on DNA, tissues and organs, but this description was not morally neutral. The way technologies were defined and described would have a direct impact on, for example, what people might consider a right. Language would, in turn, define how we decided to use or limit the technology.

Designed to build and maintain trust

Encouraging members of the public to speak their minds and providing them with substantive opportunities to do so, was widely acknowledged by workshop participants as an essential part of raising comfort levels around the application of gene editing technologies and would help to build and maintain trust in science, scientists and decision-makers.

Seiichi Toki spoke about the need for a two-way communication with interested parties, beginning from the research and development phase in the agricultural context. Openly sharing information about new cultivars species with gene editing genetic modifications that benefit farmers and consumers between the research and development community and governments, fostered a sense of trust with a broad range of stakeholders. Continuing open dialogue that had been begun in early engagement maintained and built further trust with additional stakeholders.

Krishanu Saha said that a key part of developing research priorities was having a sufficient understanding what problems needed solving. Public engagement was positioned as a means to help identify and define such problems and as well as an anti-trust mechanism that prevented monopoly over the terms of debate and descriptions of what was at stake. Given that norms for human rights, dignity and justice could shape a technology's development, and vice versa, Saha argued that the question of what was at stake should be front and centre in deliberations on how science and technology ought to shape the future. For Saha, allowing for the airing of diverse views with different, possibly competing vocabularies was a necessary step towards genuine, more inclusive solutions.

Building and maintaining public trust was understood to be about more than transparency in regulatory processes and decisions: demonstrating a desire to be transparent also required acknowledgement by decision makers of potential risks and adverse impacts. Hackett warned the workshop that failing to engage properly on potential perils might be the greatest threat to realising the technology's potential benefits. Anticipating threats and identifying actors that might challenge biosecurity, biocontainment and bioterrorism frameworks, was identified as an opportunity for the technology's proponents to display collaboration with sceptics and the concerned.

Current trends towards open science and innovation were addressed by Esvelt, who suggested that this trend could spur further development and enhance research safety. Esvelt also stated that he thought scientists bore a special moral responsibility for what they discovered or invented. According to Oye, openness, transparency and access to information, in order to inform discussion and especially to address uncertainty were important, but biosafety and intellectual property were good reasons to place limits.

The workshop's invited experts and interested parties were intent on a sensible consideration of the safe, effective use of gene editing technology. It was not an open public dialogue. As such, there was concern about finding ways to deal with a vocal minority that might hijack the conversation using an anti-science premise.

Jasanoff suggested that if a minority took a stand against a position, in a democracy we could not assume that it did this just to cause trouble. People chose to join public discussions because they felt strongly about a subject; their views needed to be addressed.

Workshop participants generally agreed that early public engagement regarding the potential uses and abuses of gene editing technologies would ultimately shape public perception, political acceptance and trajectory of diffusion for this ground breaking technology. Having experts and expert communicators engage in meaningful discussion with publics early, and iteratively, was vital to protect sound science and to enrich thoughtful deliberation. The contributions of experts in these discussions should aim to resonate with and respond to a wide range of public subsectors and concerns. Though gene editing technology was still nascent, the scientific community had already made significant efforts to engage the public, in order to explain and discuss the technology and its implications, using a variety of media forms including, but not limited to, social media videos, public lectures, TEDtalks, articles in publications targeting the general public, and podcasts (Doudna, 2015^[8]; Kahn, 2016^[9]; Synthego, (n.d.)^[10]).

6. Governance

Issues of governance include the need to foster public trust in regulatory institutions, cure high regulatory uncertainty and set reasonable regulatory standards. Governance frameworks for gene editing vary between jurisdictions, and between applications like human and non-human uses. Most workshop participants did not represent perspectives of any one nation, sector, or institution and were more concerned with relating the benefits of gene editing to those who would benefit the most. It should be noted that in some jurisdictions, such as within the European Union area, germline editing is strictly forbidden and has been for many years.

Pierre-Benoit Joly suggested that discussing international governance began with trying to reach a common understanding of the issues and with deciding whether a science-driven policy approach was valid across jurisdictions. Regulators found convergent technologies challenging to regulate. Decision-makers needed to find balance between regulatory costs and benefits, risks from accidents and restricting the technology. This balance, Joly said, had to also ensure that politically or socially restrictive environments could share the benefits.

Most participants agreed that the international regulatory landscape was now uneven, often unclear and unpredictable. Products developed using gene editing could be regulated based either on the process (i.e. regulating gene editing technologies) or on the final product's characteristics (e.g. edited livestock or foods) or both. Gene editing human somatic cells for medical purposes required careful testing both before and after the technique was applied to ensure patient safety and treatment efficacy. Rules for editing germline cells for research or medical purposes varied between countries.

In her keynote address, Jasanoff suggested a framework for democratically considering governance and how it should be applied in specific contexts. Regulating gene editing as a technological process, or its applications as therapies and products, might not be appropriate in all cases, Jasanoff asserted. As an example, sovereign countries may wish to consider non-regulatory means that might lean heavily on financial or societal measures in collaboration with entities beyond the state.

Jasanoff emphasised how, in the “international laboratory of democratic governance,” experimenting with governance tools that go beyond regulation and legislation may help to assure scientists, governments and the public that gene editing would be used when there was enough evidence that applications would be safe only.

Permission to proceed – permissible frameworks for gene editing

Most workshop participants agreed that synchronising approaches locally and globally would be better than pursuing harmonised frameworks. Several attempts to reach consensus, so as to harmonise frameworks had not succeeded fully in any area and those behind international attempts had acknowledged a need to consider broader issues in

parallel. Ideally, information on governance initiatives should be shared with public, private and non-governmental sectors, within and between countries.

Regulatory oversight of research

Jasanoff explained that the inspiration for the United Kingdom's benchmark for human embryonic research came from an ancient prayer written by late medieval scholar Thomas á Kempis. This prayer – deemed appropriate because of its connection to the Westminster-style parliament and the Church of England – was the Warnock Committee's inspiration for drawing a distinction between pre-embryo and embryo at 14 days. To this day, research on embryonic development in the U.K. was permitted until day 14 of development, after which it had to be destroyed. Several countries now used the "14-day rule" to permit human embryo experimentation (Hyun, Wilkerson and Johnston, 2016^[11]).

Japan and other countries use a range of criteria to determine acceptable use sperm ova, fertilised eggs, embryonic stem cells and induced pluripotent stem cells. Embryos can come from a range of sources that include surplus embryos from IVF, non-viable embryos from IVF, or embryos generated specifically for experiments. Extending the use of human embryos beyond this 14-day benchmark above other issues will, from a technological perspective, depend on the accuracy of gene editing systems used to edit germline targets.

In Sweden, Lanner's use of editing to disrupt genes in developing embryos was permitted under the Genetic Integrity Act. Because of a permissive research environment, Lanner's research received approval in 2015 by the Central Ethics Review Board. The experimental embryos his lab used were a surplus from IVF treatments, were permitted for basic research only and re-implanting them was strictly prohibited.

Germany, in contrast, prohibits human embryo research by the Embryo Protection Act. Surplus embryos must not be used for research and embryos must not be created specifically for research. German legislators have allowed preimplantation genetic diagnostic (PGD) for severe hereditary diseases only.

Canada also prohibits experimentation on human embryonic stem cells under the 2004 Assisted Human Reproduction Act. However, Canadian academics urged the government to reconsider this framework due to developments in science and society developments since it had been enacted (Knoppers et al., 2017^[12]).

The moratorium on germline editing, Saha said, treated basic and applied sciences as separate worlds and stifled conversations about what technological futures could be in the making. It also reduced ethical questions to matters of safety and efficacy, or lumped researchers working on the pro-social uses of the technology together with bad actors. He further believed that ethical discussions should be held on an international level.

Most participants agreed that across all areas of application conventional risk analysis frameworks may require adjustments to better capture the changing scenarios presented by gene editing technologies and alleviate public concerns. In cases where socio-economic risk assessment frameworks are considered, potential benefits to society should not be neglected in the analysis, and in cases where negative results could not be proven, consideration of theoretical risks against potential benefits, risk of inaction and uncertainties may lead to a balanced position.

Clinical applications of gene editing in humans

At the time of the workshop only a single patient in the United Kingdom had had her genes edited, using the TALEN system.⁷

In addition, in the United States, the National Academy of Science and National Academy of Medicine recommended that gene editing research continued and considered possibly allowing germline editing in the future under strict conditions (National Academies of Sciences, 2017^[13]). In contrast, Canada has published discussion documents citing a need for further deliberation about appropriate mechanisms, oversight and considerations for using gene editing in humans (Canadian Institutes of Health Research, 2016^[14]). Austria, Italy, Spain and the Netherlands have enacted bans for human germline editing. India and other countries plan to hold deliberations on using human gene editing in 2017.

At the time of the workshop, many nations had prohibited or placed moratoria on human germline editing, because a lack of safety and efficacy data seemed to preclude human clinical trials.⁸

Regulations for non-human gene editing

Existing governance structures share considerations for a need to use gene editing judiciously in live organisms, especially humans. However, just as some countries permit or prohibit embryonic stem cell experimentation based on their societal constructs, some show low or high acceptance for genetically modified organisms.

In his keynote speech, Hackett spoke of governments' role in regulatory development, and observed that gene editing technology had evolved at a pace faster than that for Moore's law (i.e. technology doubling every two years). Hackett recommended that decision makers consider three statements:

1. The trillions of taxpayer dollars that had been invested in research had returned little tangible benefit. Gene editing could provide tangible benefits.
2. Each person on Earth should be able to benefit, not just those in wealthy countries.
3. Regulations should consider the strides the biological sciences had made since recombinant DNA technologies had been developed.

The public in many European Union member states showed low acceptance for genetically modified organisms, although gene editing's advent had prompted the EU to revisit its GMO framework. Hackett pointed out that while gene editing could be used to create GMOs, it could do far more, and he questioned whether edited organisms and GMOs should be regulated in the same way.

In the Europe Union, the European Court of justice had deliberated the use of gene editing in plants for more than two years. France's industrial stakeholders had been vocal in their views requesting strict approval regimens for gene edit products, while the Netherlands supports excluding gene editing from GM regulations. Significant political sensitivities mean no decision was expected until 2018. In the meantime, Sweden and Finland have opted not to regulate gene editing in plants, but would reverse this decision, if the court eventually ruled in favour of regulation.

A case description of governance approaches in Japan is given in Box 6.1.

Box 6.1. Case description of gene editing governance: Japan

Two presenters from Japan gave insights into the Japanese context, in which gene editing experimentation has flourished. Seiichi Toki said Japan had made deliberate efforts to promote a social understanding of agriculture biotechnology, especially gene editing. As Japan had signed the Cartagena Protocol, appropriate control based on the Cartagena Act which regulates living modified organisms was required, with which its transgenic and gene edited crop experiments comply. Cultivating any such crops or using them for use in food or feed would therefore require prior consultations with appropriate regulatory agencies for approval.

Hidegori Akutsu spoke to an interim report on research using gene editing technology on human embryos: the national context in Japan permitted and encouraged the use of advanced technologies, including gene editing in humans. However, in 2015, before permitting widespread use, the Japanese Expert Panel on Bioethics had been convened to ensure that governments and academic societies developed strict rules for using gene editing in humans.

Japan's context derives from its 2004 policy on producing human embryos for research purposes. In principle, human embryos cannot be created for research unless it met four criteria:

1. Scientific significance in life science and medicine cannot be obtained other than through the use of human embryos.
2. The benefits or anticipated benefits are socially appropriate.
3. Assurance of human safety [are made].
4. Safeguards must be place to avoid raising concerns of reducing human beings to tools or means.

Three additional guidelines cover different levels of research use:

- Permitted use to create embryos and in assisted reproduction technology research
- Permitted use for human embryonic stem cells
- Prohibited use for embryonic gene therapy.

The interim report builds on the 2004 policies by positing that if new research for congenital incurable diseases was proposed in the future, social acceptance had to be considered using fundamental principles. These principles distinguished adult versus embryonic stem cells and induced pluripotent stem cells versus zygote or germline cells. Induced pluripotent stem cells with genome edited modifications could potentially be re-implanted in the individual from whom they are derived, but would not be expected to transmit genomic modifications to future generations. Zygote or germline cells, on the other hand, held the potential to transmit genetic changes to future generations.

The Japanese interim report's recommendations include:

- Prohibiting germline editing for clinical use, due to unresolved issues
- Studies that may contribute to understanding genetic function in early development and organogenesis.

However:

- Surplus embryos (not those intended for clinical use) can be used.

- The handling period for human embryos must be limited to the early embryo before the primitive streak forms, so only up to day 14.
- Human embryos used in research must also be disposed of securely.

The Japanese Expert Panel on Bioethics final report was intended for release in 2017.

Source: Presentation by invited experts from Japan, Ottawa, September 2016.

Workshop participants came only from wealthy developed nations, but considered impacts of gene editing applications on developing nations and urged their inclusion in deliberations. Using gene drives to eliminate vector-borne diseases such as malaria, dengue fever and Zika virus would have a major impact on populations of nations, where they are deployed. Crops edited to tolerate temperature extremes or livestock that grow faster and yield more would improve food security.

Achee's gene drive research and Thizy's public engagement work are examples of co-creation with developing nations. Achee said that for her research, minimum clinical and field trial standards had to be met, biosecurity thresholds had to be established and human ethical review boards had to be involved. Gaps in governance structures created opportunities to build capacity and partnership, and co-created and advanced processes in phases, in order to fund projects like the one she presented. Structures and processes including oversight committees, needed assessments; technological training and infrastructure were also needed along with practical opportunities for developed and developing nations to cooperate and share practices.

Patient advocates, minority advocates and other groups that in earlier times have had solutions given to them could be partners in co-creating appropriate solutions, an idea summarised as, "Nothing for us, without us." Conversations about gene editing benefited from actively soliciting, including and hearing voices from developing nations, minority perspectives and those most likely to be affected.

6.1. Towards good governance

The workshop discussed current regulatory frameworks and other types of governance structures that were currently in use or that could be deployed in the future, rather than deliberating the relative merits of existing systems. The focus was on the questions decision-makers could ask to help develop appropriate governance frameworks for gene editing; these included:

- What should we govern – the technology or the applications?
- What criteria should we use?
- Who should govern?
- Who should develop criteria for governance?
- What mechanisms, institutions and processes should we use?

Governance discussions covered roles of governments and international organisations mandated with convening and discussing multilateral issues. However, non-regulatory entities such as transnational professional organisations and intellectual property arrangements also had roles. For example, research funding agencies, journal editors and institutional ethics boards might informally enforce guidelines developed by professional scientific societies.

Governance affected public engagements and decision makers' mandates might limit pursuit of certain kinds of information and public engagement. Collaboration and cooperation between governance structures would help to frame issues and ensure that public engagement yields nuanced, detailed data with which to develop regulations.

The intersection between governance and public engagement was explored by Zilberman, who said that there was a need for greater education for farmers and the public, in order to have meaningful governance discussion. In addition, liberal, risk-based regulations and adaptive learning that would allow technologies to move ahead and be revaluated based on evidence generated by use, rather than restricting them at the beginning, would be needed. Support for applications that had environmental elements, such as payment for greenhouse gas emissions, were as necessary as patience and persistence.

Regulatory compliance

Participants discussed whether international harmonisation might offer ways to address complex gene editing issues and governance in areas with multinational implications. There was a sense that harmonising governance mechanisms could be useful, but each jurisdiction had to consider whether this was appropriate in its own context.

Oye suggested that most areas of international affairs needed a large disruption or crisis to create the pressure to clarify what shared interests overcome national interests. In the laboratory of democracy, Marchant suggested, there was value in trying different approaches. Oye questioned how regulatory differences could be based on scientific knowledge, and whether the data that justifies different regulatory approaches was tested properly.

Hackett illustrated the contradictions that some regulations might pose using the example of human food consumption. Most people, Hackett said, ate 10 000 billion genes per meal, knowing little of the individual genes, much less their possible interactions. Information about these genes and their products was scarce, as was evidence about the long term safety or health effects of the foods they come in. Yet, genetically modified organisms produced for food required significant evidence for approval. Since gene editing could be used to re-introduce native or "wild-type" genes, Hackett questioned whether the same levels of evidence would be required for gene edited products and GMOs. He added that the data that regulators requested for evaluation had little value, because regulatory frameworks were generally "stagnant", "outdated" and "incapable" of responding to exponential technological innovations.

Applying the precautionary principle

Zilberman said that applying the precautionary principle – used by some government regulators – sounded like a good idea, but it worked against the logic of science, where one adjusted as one generated and applied more information. For new technologies it might be reasonable to proceed with applications and continue, where outcomes are favourable, but stop otherwise. The idea that we had to know all the risks before moving forward, which was how many interpret the precautionary principle, could reflect both a lack of public trust and an attempt to stop a new technology.

With genetically modified foods, for example, Zilberman showed that where no mechanism existed to reconcile modern technological advances with social constructs of what we consider "natural", the resulting regulatory framework proved deficient. Only large companies had the resources to steer through the regulatory system, reinforcing the

idea that the technology was for corporations, not for people. Zilberman observed that despite hurdles and a negative public image, developing biotechnology for agriculture had had positive results, including higher yields, less need for pesticides, lower costs and a better quality of life for farmers. Farmers in developing economies who used GMOs benefitted more than those who did not. Zilberman suggested that participants considered the risks that came with not using gene edited crops to address grand global challenges, such as food security and vector-borne disease; he pointed out that we needed to cooperate on developing oversight frameworks in collaboration with those that might benefit from the technology.

Toward harmonisation?

“Maybe we should not aspire to a homogenous approach, but embrace that we live in a ‘pluriverse’, not a universe.” (Pierre-Benoît Joly, French Institute for Research and Innovation in Society and French National Institute for Agricultural Research, France)

Non-regulatory measures could include allowing a country to accept technical data generated in another country. Jasanoff challenged the audience to consider that there were societal ideas about whether something was natural or not, whether citizens were willing to live with things that cross the boundaries of what they would consider moral, right, or natural. Here the term “harmonisation” was not appropriate, she suggested. Political actors have been known to respond when certain aspects of their sovereignty were curtailed as a result of belonging to a global community.

Hackett urged caution toward harmonised approaches, since developing and developed nations may not agree on the rules for technologies, local entities might want to use the technologies ways that differed from those of large corporations. Developing frameworks for harmonisation required an understanding of how “unlike” nations would use applications, as well as how “like” nations would use them.

Lanner suggested that requiring regulatory harmonisation for experimental research could be dangerous; frameworks instead should build in enough flexibility to accommodate different contexts. For clinical trials though, global agreement was preferable. Global clinical trial frameworks beyond the Declaration of Helsinki could be particularly useful for gene editing applications to address rare diseases.

Policy decisions could be made at different loci – executive legislatures, appointed councils outside of conventional politics, or others. For gene editing, Jasanoff said, jurisdictions had to discuss not only risks and benefits, but also the nature of life, what we owed its sanctity and where reason fitted into the judgement.

Jasanoff added that the harmonisation of standards for commercial products was different from harmonisation of what kind of persons one wanted to have in the world.

7. Innovation policy

Despite the patent thicket that some workshop participants perceived to surround gene editing technology, Zilberman pointed out that the number of start-ups and research institutes that depended on gene editing technology continued to increase. However, gene editing was not only an “innovation” in itself; it was likely to enable a broad spin-off of innovations with significant social and economic impacts.

“Access to enabling technology is key to innovation; the more access for free, the better.” (David Zilberman, University of California Berkeley, USA)

7.1. Intellectual property

Zilberman noted that, in the United States, constraints on intellectual property could be overcome partly by selling or trading rights. There, the Public Intellectual Property Resource for Agriculture was a clearinghouse for intellectual property and could give access to developing countries, but many projects currently failed due to a lack of access to intellectual property rights.

Inventions, Zilberman said, might be created in universities or other institutes of learning, but the public sector was needed to develop the technology. The private sector would not proceed until there was a possibility to market the product – it wanted regulatory certainty. For example, small and medium enterprises that researched niche crops were not attracted to GMOs, so the technology concentrated in the hands of large companies that used it to develop major crops.

Zilberman argued that technology barriers did not hurt the poor as much as financial and regulatory barriers did. So, it needed to be asked: “What risks come with doing nothing with a technology?”, and “In what contexts will regulations for it be developed?”

Several participants cautioned that regulation for gene editing had to not parallel decisions that were made for GMOs, because costly compliance and regulatory schemes would concentrate another potentially-world-altering technology in the hands of the few. Costs and barriers, when low enough, could permit a wide range of actors to use the technology, if determined to be safe and acceptable.

Patents served a variety of functions, Dianne Nichol (University of Tasmania, Australia) noted. Beyond excluding competitors, they:

- serve a disclosure function
- raise revenue
- set boundaries around work
- create opportunities for collaboration and sharing through exclusive, non-exclusive and mixed licensing and pooling or aggregation with other players
- serve a dispute settlement function, as does cross-licensing.

However, according to Nichol, they also can:

- raise fears of litigation
- increase the likelihood for project abandonment
- disrupt collegiality, collaboration and objectivity
- decrease access and raise cost, especially for clinical diagnostic testing
- decrease quality
- prevent second opinion testing
- lead to highly fragmented property landscapes which can increase search and transaction costs, if obtaining different patents from many property holders are necessary for commercial development.

Robert Cook-Deegan (Duke University, USA) challenged the workshop to reconsider the existing concept of linear pipelines for product research and development: policies now presumed that the public sector funded and developed innovations, which were then handed off or licensed to the private sector, which commercialised them. In reality, the process was less than linear, and patent incentives did not end when academia handed off a patent to industry.

Cook-Deegan argued that creative patent dispute resolution and deployment mechanisms from the past can still work in the present. Cohen-Boyer, one of the first biotechnology patents to shape current norms had been granted to Stanford University in the 1970s, when the idea of patenting recombinant DNA had been highly controversial. History pointed to this as a milestone for patents for products generated by publicly funded scientific research. Stanford University licensed its recombinant DNA technology using the following four guides for its use: A proposal had to:

1. be consistent with the public service ideals of the university to promote and disseminate knowledge
2. hold incentives appropriate for commercialising genetic engineering technology for public benefit
3. avoid biohazards – the patent could be used to stop applications of the technology that would violate the National Institutes of Health guidelines
4. generate income for research and teaching.

This first biotechnology patent had shaped current patent discussions and shown their value, but there were other ways to get important things done, as with penicillin and the polio and smallpox vaccines.

By contrast, Cook-Deegan used the examples of the human papillomavirus (HPV) vaccine and Hepatitis C drug to show that the R&D pipeline and patent frameworks could succeed, while deploying them did not. Assessments showed their positive impacts on healthcare systems; but they were simply too costly for many jurisdictions to be able to use widely. Whether these treatments reached their full potential for population health nationally or internationally was a question that remained to be answered. Those who wished to follow this model for research, development and deployment needed to identify and understand the barriers that barred widespread deployment despite their great promise for addressing global grand challenges.

Dianne Nichol said patents were neither good nor bad in themselves. Discussions surrounding patents were often about early decisions made without full knowledge of the implications; it was important to know what one hoped an open and transparent patent or technology would achieve. She reminded the workshop that patent rights were granted

within jurisdictions, albeit according to international standards. Patent decisions would affect strategic decisions about where to invest. Companies usually succeed based on the length and strength of their patents.

The United States CRISPR patent dispute and resolution

Summarising his thoughts on the CRISPR patent dispute as it stood at the time, Cook-Deegan said the United States' court decision would affect many of the 2600 CRISPR related patents pending. Contrasts between the patent decisions made about recombinant DNA in 1980 and CRISPR in 2017 were clear, and the implications were clear as well: IP affected what was happening in science and what applications would be available to all of us. The CRISPR patent dispute would be resolved in one of two ways, Cook-Deegan said: one was fraught with logjams and obstacles on the licensing path, while the other was to “play nice”. Scientific reputations and the range of applications available to all of us were at stake, if the deployment of this technology was mishandled.

At the time of the workshop, the CRISPR/Cas9 patent dispute had not been resolved.⁹

A recent communication from MIT and the Broad Institute reiterated that CRISPR itself cannot be patented. Instead, the application that was granted relates to “engineered components and compositions specifically altered from their naturally-occurring form to be useful in methods for editing the genomes of living mammalian cells.” CRISPR-related patents have been granted around the world.

7.2. Regulatory impacts on innovation

Regulatory impacts on innovation will depend on their context. In considering whether or not the Harvard onco-mouse was patentable, the Canadian Supreme Court reached a ruling opposite to that of its American counterpart, based on a law containing almost the same language, Jasanoff reminded. The differing responses were rooted in the fact that the American jurisdiction considered the mouse as property and the Canadian jurisdiction considered it as life.

Changing its regulatory frameworks is costly for any jurisdiction. But any jurisdictions doing gene editing research – as supporters of innovation or as targeted users – have to review their regulations to decide if and how to adapt to address scientific advancements in ways that do not stall innovation, taking into consideration that what does not happen in one country, will likely happen in another. For gene editing to reach its potential, Joly suggested that innovation in complementary areas such as genomics, synthetic biology and metabolic engineering had to also advance; without them, experimentation and commercialisation might stall.

As scientists refine gene editing systems, the ways that governments will assess risks of using the different delivery mechanisms, gene editing machinery and guide RNAs will gain from shared information and frameworks regardless of regulations. How these critical parts of gene editing systems are patented will also be an area of international interest.

Marchant focused on considerations unique to human applications, including regulatory and scientific issues that should be considered as risk assessments, governance and scientific issues were sorted out. Countries used different frameworks to assess drugs, biologics and devices, based on whether the technique was *in vivo* or *ex vivo*. How gene editing components and technology were classed may be key to understanding how to

regulate them for medical purposes, but went into a level of detail that would not serve the public. Patent frameworks would affect and be affected by the ways one classed the technology, components and delivery mechanisms.

7.3. Innovation and global grand challenges

Reasons for funding science in the areas of human health, agriculture, aquaculture and environmental issues vary, but there is often a common thread, or a common tangent to one: addressing global grand challenges. Dealing with disease, infection, food insecurity and others are largely agreed to be reasonable investments for public funds. Sylvain Moineau's initial CRISPR research was largely paid for by Canadian public funding. While his research may not have begun with a wish to address global grand challenges, it is true that the applications that have risen from his work can, under a balanced intellectual property framework, have a positive impact on those grand challenges.

Innovations can spur intellectual property disputes. Zilberman noted that some governments could intervene legally when companies refused to settle disputes reasonably. Forcing companies to settle disputes by this means was an intriguing option for innovations funded by the public, or intended for the public good.

Nichol said that if gene editing innovations were to progress, it was important to answer questions of what property should be protected and what should be shared, using consideration and wise approaches to global harmonisation, regulation, governance, education, communication and public consultation. Going forward would take clear understandings of all actors' roles and responsibilities in the system – including their drivers.

8. The context of gene editing

Understanding gene editing in context was a theme visited throughout the workshop, starting with Sheila Jasanoff: individuals, groups and nations would use attributes and values from particular contexts to help them understand gene editing and subsequently make decisions regarding its application.

It is important to understand the basic context of these discussions. Are we in the midst of a revolution, or experiencing a “breathless moment”? Revolutions, said Ken Oye, happened in part due to timing and gene editing, specifically CRISPR/Cas9, merited the attention it had gained because the context and time were ripe. The tool was enabled by the technological advances that preceded it, including advancements in high throughput DNA sequencing, information technology and information management, DNA synthesis and gene editing tools.

Or, are we witnessing a moment, where media is declaring a breakthrough or radical change in the absence of sufficient data? Each of these descriptions is in fact comprised of ethical and moral statements based on factual claims. Whether gene editing is a bright revolution or a quick flicker remains to be seen, but it still raises many significant issues in a complex landscape.

Given the interconnectedness of humans, agriculture and aquaculture and the environment, impacts in one area of application may have significant repercussions across other sectors and at other levels of governance. Gene editing and its applications were considered in several contexts by workshop participants. Scientists discussed the mechanisms of gene editing in the context of DNA sequence and on- and off-target efficiencies. Other scientists focussed on the impact of gene editing on the cells, organs and tissues of an organism. Regulators are also interested in these mechanisms because they provide safety and efficacy data. Some participants discussed gene editing in the context of species populations, ecosystems and the environmental implications. These were also of great interest to regulators who consider the implications of their regulatory systems. Layered upon all of these focal points were suggestions by participants to consider the societal constructs of ethics, morals, values, politics, religion, etc.

9. Uncertainties - questions that need answers

Questions raised and discussed at the workshop have wide-ranging ethical implications; many of which were perceived as “unusual” or even “uncomfortable”. The underlying perception is that gene editing may offer the human species the power to control its own evolutionary history.

All workshop presenters acknowledged the reality that decision-makers have been challenged with basing decisions on detailed, but often times incomplete, information and nuanced knowledge of the context, in which they function. Together, these factors will ultimately impact the trajectory of their respective frameworks for gene editing and can affect other jurisdictions through trade, tourism, geography or other means. Simply deciding what is or is not presently plausible, or what development may be short-term or far off, may lead to oversimplified regulation and governance. Such oversimplification may truncate or delay deliberations on important questions until they are urgent or it is too late to act; they may also lead to knee jerk decisions or patch-work solutions that have unanticipated and significant consequences.

Before gene editing applications can be broadly deployed, decision-makers will be faced with decisions on defining the difference between critical concepts such as “therapy vs enhancement”, or “normal vs pathological”. Furthermore, jurisdictions may not agree on where to draw these lines; this idea is depicted in Figure 9.1.

Figure 9.1. Opposing issues raised by gene editing

Note: Findings from the international workshop: Opposing or continuous ideas and the image of a spectrum in which individuals and nations will determine where they are placed based on the thickness of descriptions and the contexts in which deliberations are held. Individuals, publics and nations will determine where to draw these lines based on their contexts which include politics, values, culture, geography, knowledge, legal frameworks, morals, etc.

Source: Canadian Delegation to the BNCT, April 2017.

The scientific questions that remain and prevent widespread deployment of gene editing applications are complimented by questions that participants had no clear answers for. These arbitrarily categorised questions were raised or inspired by conversations and presentations and will likely be raised in any jurisdiction challenged with considering applications of gene editing; these questions include, but are not limited to the following:

Categorising medical treatment

- Where do we draw the line between somatic and germline therapy?
- When is gene editing in humans considered a preventative measure, therapy or enhancement?
- Is prevention using gene editing considered a therapy, enhancement or a new category?
- What are the criteria of “normal” variants versus pathological or non-native?
- How strictly should germline editing be controlled in somatic applications?
- How long should edited cells stay in the body?

Technology assessment

- How should we define “risk” and “benefit”?
- What are short-term benefits? Long term scenarios?
- Since sexual selection introduces more mutations than gene editing, what threshold should be set for accepting off-target mutations or mosaicism?
- How can (or should) we consider the effects of non-gene editing mutations and/or epigenetic changes?
- What kind of risks might edited cells impose on a patient?
- Formal risk-benefit-uncertainty analyses exist for regulation, but do these work well in conditions of social controversy and scientific uncertainty?

Research

- What differences distinguish basic and applied research into gene editing?
- How should we consider animal welfare, subject selection and trial design for human applications?
- What should the research community do to fill in gaps while the public sector lags?

Innovation and commercialisation

- How should trade secrecy or data transparency apply to gene editing research and uses?
- How do competitions between ideas and businesses affect the introduction of a technology?
- Informal risk-benefit-uncertainty ideas – that is, hype – could harm scientific advancement if the hype is not fulfilled. How can we create accountability?

Issues for public discourse

- How can the perspectives, needs and opinions of individuals be resolved with those of broader societies?

- How can governments resolve the ways that the lay public and experts receive information?
- Who should define what is a risk and what is a benefit?
- What kinds of discussions should be taking place at the national and international levels?
- What social, economic and political contexts should we use to define risks and benefits, nationally and internationally?
- When the clinical goal is to restore “normal” function, who decides what is “normal”?
- Does an individual have a right to choose to be edited?
- Do individuals have a right to know when they have been edited?
- Do current approaches to language and analysis appropriate to inform a full discussion of risks, benefits and uncertainties?
- Are there cases where the lay public gets information in different ways than experts?
- How do we create accountability, if informal risk-benefit ideas can harm scientific advancement when hype is not deserved?
- How does a developed economy differ from a developing economy? Should gene editing be used differently in each?
- Is the ability to have biological children a human right?

Concerns unique to applications in agriculture and aquaculture

Key questions regarding gene edited organisms for agriculture and aquaculture involve managing the effects of these organisms on and in the environment. In some jurisdictions, risk assessment frameworks already in place for identifying and assessing risks, benefits and uncertainties of previous applications of biotechnology are well positioned to accommodate gene edited plants and animals used for agriculture and aquaculture. These well-positioned frameworks tend to regulate products on the basis of their attributes rather than on the question which technologies were used in the production process. Where jurisdictions employ process-based risk assessment frameworks, difficult decisions are made regarding regulatory triggers and appropriate levels of regulatory oversight. It may also be difficult for these jurisdictions to keep pace with the rapid advancements in modern biotechnologies going forward.

Concerns unique to human medicine applications

Applications of gene editing in humans give rise to unique considerations. Chief among these considerations, as highlighted by Gary Marchant, is the practical need to clearly distinguish somatic applications from germline; and therapeutic uses from enhancement. Many countries appear to be comfortable with somatic applications such as gene therapy and using recombinant DNA does not appear to raise new issues. However, using gene editing in germline cells or for enhancement is much more controversial. The regulations that govern stem cells and human embryos are not internationally harmonised. The Convention on Human Rights and Biomedicine (“Oveido convention”) is an important multinational agreement, which addressed germ line interventions, though it is applied in certain European nations only.

Marchant also questioned whether unique approaches to govern human foetal gene editing might be warranted given that treating some genetic conditions required

intervention or modification prior to birth and that these might be transferred to the germline.

Zeller suggested that somatic genome editing would happen soon, likely using an in vivo delivery mechanism, retroviral vector, or an ex vivo technique that included cell culture.

Criteria that may be used to assess the risks for gene editing interventions remain unclear; for example:

- What will be the clinical trial requirements?
- How many patients should be included?
- How should “off-label use” be treated?
- In jurisdictions where it could be possible, should doctors eventually be able to prescribe gene editing at their discretion, simply by writing prescription as with other drugs?
- How would individual gene editing affect public health?
- What impacts would gene editing interventions have on health care systems?

Concerns unique to environmental applications

Unlike gene editing applications in human medicine, applications in agriculture and aquaculture, environmental applications will be designed to be released. Containing gene edited products are important for aquaculture and agriculture and less so for intrinsically uncontained applications such as bioremediation, biomining and controlling invasive species. However, the need for containment and biosafety is significant during research and development, where release of or exposure to uncontained environments is undesirable.

Edited microbes can be used for synthetic biology applications, where orthogonal systems can limit lateral gene flow, if the organism is released. Oye gave an example of an organism designed with multiple nutrient dependencies that included synthetic amino acids. These unusual needs would limit the organism’s environmental distribution and impact and in fact render it unlikely to survive in nature.

Gene drives are created with the intention of releasing them into the wild. But modelling wild release is very tricky, which is where local gene drives can be particularly useful. In the case of white-footed mice with Lyme disease, or mosquitoes with malaria, the approaches have been designed judiciously.

For example, Achee’s work focused on 20 mosquito vectors found in Indonesia, which were all similar genetically, but which differed in specific behaviours. Indonesia was selected for local gene drive trials because of its geography and because it has the highest incidence of malaria outside of Africa. Children and youth are at the highest risk of death and survivors’ quality of life is reduced. Two published proof-of-concept studies suggest gene drives in mosquitoes showed promise, but need to be optimised for off-target effects and vector hotspots. Sumba Island, near Bali, has been selected for a Phase 3 trial to measure the entomological and epidemiological effects, where full reseal in different areas has occurred. This data will help researchers measure success.

Esvelt pointed out that only three species of *Anopheles* mosquito were linked to the spread of malaria in Africa. Achee said that it would be important for gene drive researchers to consider how the target sequence or guide RNA was conserved across genera, species and related strains. It was possible that a gene drive intended to be local could produce global impacts if researchers did not stay diligent.

Workshop participants identified issues and questions arising from discussions that may require further analysis, to determine if OECD countries have common or divergent assumptions, what the assumptions are and whether they are valid. The OECD was identified as a possible lead for providing guidance on the issue regarding intellectual property (IP) arrangements, given its influential prior work on licensing genomic inventions.

Issues for future development

Throughout the workshop, participants identified a number of areas for future research and deliberation, including:

- how ethical issues are handled across jurisdictions; especially for scenarios with broad economic implications
- understanding existing institutions and practices of public engagement
- the role of “open science” in gene editing research
- the role of patents as a tool for governance, where limits for responsible research and innovation are written into licensing agreements.

Potential future questions include:

- Should the bar move from a moratorium to allow gene editing human embryo research within a specified number of days or weeks of development?
- Should gene edited products be considered different than genetically modified products?
- What compassionate medical uses raise sufficient grounds to allow gene editing applications?
- How do we increase literacy in gene editing science, ethics and social issues among general society – not just elites?
- What kinds of gene editing regulatory practices garner public trust?
- Can the work of social scientists to help ensure that public engagement is culturally sensitive and adaptable to local contexts?

In the context of governance, there would be utility in understanding different approaches to governance in member countries, as well as evaluating risk analysis frameworks that member jurisdictions intend to use for gene editing applications. Additional issues regarding gene editing technologies, and the questions and where open and transparent discussion may be needed to fill knowledge gaps and improve equity among members include:

- mechanisms for including ethical and social considerations in national and international decision-making processes
- gap and needs analyses to compare technology uptake in developed and developing economies
- strengths and weaknesses of approaches to the governance for emerging technologies, including how different systems cope with rapid technological changes.

Possible future questions include:

- Are different categories of risk analysis needed for different gene editing applications?

- Are the de novo risks associated with gene editing technology in agriculture and aquaculture beyond those associated with conventional breeding strategies?
- Will a harmonised approach be needed for trade?
- If developing nations lack adequate regulatory frameworks, who should decide on the safety or value of gene editing projects?

Regarding the impact of gene editing in the broader context of Science, Technology and Innovation (STI) policy, questions and issues that may be in need of attention include:

- Can government and regulatory science keep pace with the advances in the private sector?
- What gaps in regulatory research support the scientific risk assessment of gene editing technologies?
- What kind of regulatory science needs to be completed for compliance and enforcement activities?
- Can gene drive research that is not conducted with openness be discouraged by preventing publication?
- What principles can we develop for open science in pursuit of global development and health goals?

Lastly, in discussions about gene drive technology, most participants were in general agreement about stringent containment measures for all gene drive research; this could only be relaxed in consultation with regulators, as, for example, recently mandated in the Netherlands. Until sufficient evidence was produced, these stringent containment measures were needed to mitigate irreparable harm. Most workshop participants also agreed that public investment may be needed for regulatory and policy research, and technical environmental safeguards to limit lateral gene flow.

Notes

- ¹ CRISPR/Cas9 stands for “Clustered Regularly Interspaced Short Palindromic Repeats” associated to a Cas9 protein
- ² TALEN stands for “Transcription Activator-Like Effector Nucleases”
- ³ ZNF stands for “Zinc-Finger Nucleases”
- ⁴ Since this workshop, data on these cattle have been submitted to the United States Food and Drug Administration for review.
- ⁵ Since the workshop, the United States’ National Academy of Sciences and National Academy of Medicines published a report that suggests a future for germline editing – with stringent conditions (National Academies of Sciences, 2017_[13]).
- ⁶ Following this workshop, Thizy and Target Malaria held a workshop with the West African Economic Community in October 2016. Discussions covered differences between regulators and ways to collaborate and harmonise these where appropriate.
- ⁷ Since the workshop, both the People’s Republic of China (hereafter “China”) and the United States have permitted gene editing clinical trials in humans (Cyranoski, 2016_[16]).
- ⁸ Since the workshop, gene editing technology has developed rapidly and significantly, with the United States and China announcing human gene editing clinical trials in January 2017 (Cyranoski, 2016_[16]). China at first said its scientists would use only non-viable embryos in gene editing experiments; however, a lack of success with experiments on non-viable embryos led China to begin using viable embryos for gene editing demonstrated in publications since the workshop (Tang, Zeng and Du, 2017_[17]).
- ⁹ Since then, a judicial board of the US Patent Office has handed down a ruling that can be considered favourable for the Broad Institute/MIT patents, but an appeal against that decision has already been filed (Cohen, 2017_[15]). In contrast the European Patent Office has granted a key CRISPR patent to the UCLA and the University of Vienna in April 2017. Since, American courts have ruled in favour of the Broad Institute/MIT patents, but appeals remain possible. Whether today’s patent frameworks are good for development of science and technology is a question of national and international importance.

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ANNEX A: Workshop Agenda

Working Party on Biotechnology, Nanotechnology
and Converging Technologies (BNCT)

Directorate for Science, Technology and Innovation

This workshop aims to stimulate a wide-ranging discussion that involves scientists, business leaders, policy makers and opinion leaders. It will be a cross-disciplinary event to exchange information and approaches across countries on the science, governance, and economics of gene editing innovations in:

- Applications in Agriculture & Aquaculture
- Environmental Applications, and
- Applications in Human Medicine.

Working through breakout sessions and case studies, the meeting will highlight policy issues of applications in each sector. It will also explore the important issues shared across these sectors that are critical to economies, including issues of science policy, innovation and governance.

In addition, the workshop aims to address certain economic questions raised by gene editing, notably IP issues and business and financing models, with a view to highlighting important aspects of responsible commercialisation.

Workshop on Gene Editing in an International Context: Scientific, Economic and Social Issues across Sectors

29 – 30 September 2016

Sir Frederick G. Banting Building
at Tunney's Pasture*

*251 Sir Frederick Banting Driveway, Ottawa, Ontario, Canada K1A 0K9

Attendance of this workshop is limited to OECD delegates and delegate-nominated experts.

To register for this workshop, please contact steffi.friedrichs@oecd.org, stating the name of the relevant delegation.

Synopsis (continued):

The workshop will highlight and discuss the current trends and technology realisations in each sector and give an overview of what the new technology development may bring, and where different issues of controversy and safety across different expertise fields lay.

The developments of gene editing will be viewed against existing governance structures and common policies. Issues around ethics and social responsibility throughout the research and innovation process for new diagnostics, therapies, and technologies will be raised and discussed. Here the goal of good policy should not just be deployment, but socially responsible development in accord with public values so that economic and health benefits can be realised and trust in science and governing institutions preserved. Emerging codes of conduct and other governance mechanisms will be discussed with a view to clarifying elements of a common framework and shaping future development.

PRELIMINARY AGENDA

TIME	
8:00 – 8:30	Bus Transport to Workshop Venue: Buses will leave from the Lord Elgin Hotel at 8:10
DAY 1: THURSDAY, 29 SEPTEMBER 2016 Plenary Sessions (Location: Banting Theatre)	
8:15 – 9:00	Registration/Arrival
SESSION 1: Welcome Co-Chairs: Pierre Sabourin & Andrew Atkinson	
9:00 – 9:10	Welcome by the Host Speaker: Terry Beech, Parliamentary Secretary to the Minister of Science, Canada
9:10 – 9:15	Welcome by the BNCT Secretariat: Presentation of Workshop Outline Speaker: David Winickoff, OECD BNCT
SESSION 2a: Setting the Scene - Key-Note Presentations on Gene Editing Technologies and Issues Co-Chairs: David Winickoff & Andrew Atkinson	
9:15 – 10:00	Key-Note 1: <i>Global R&D in Gene Editing Techniques / The Technological Break-through of Gene Editing: Past, Current and Future Developments</i> Speaker: Perry Hackett, Recombinetics, USA
10:00 – 10:45	Key-Note 2: <i>Editorial Discretion: Texts and Contexts of Human Genome Editing</i> Speaker: Sheila Jasanoff, Harvard University, USA
10:45 – 11:15	BREAK
SESSION 3a: Case-Studies in Gene Editing Technology and Innovation Co-Chairs: Steffi Friedrichs & David Trus	
11:15 – 11:45	Innovation Case-Study 1: <i>Responsible Research in Gene Editing: Eliminating Malaria</i> Speaker: Nicole Achee, University of Notre Dame, USA
	Innovation Case-Study 2: <i>Genome Editing in human Embryos: A Tool to gain fundamental Knowledge in early human Development</i> Speaker: Fredrik Lanner, Karolinska University, Sweden
	Innovation Case-Study 3: <i>Flax Advanced Breeding: Using true Gene Editing for the first Herbicide Tolerance Trait</i> Speaker: Greg Gocal, Cibus, USA

TIME	
Plenary Sessions (Location: Banting Theatre)	
... continues:	
SESSION 3a: Case-Studies in Gene Editing Technology and Innovation Co-Chairs: Steffi Friedrichs & David Trus	
11:45 - 11:55	Innovation Case-Study 4: <i>Genome Edited Plants in Agriculture</i> Speaker: Toki Seichi, National Agriculture and Food Research Organisation, Japan
11:55 - 12:15	Panel Discussions of Innovation Case-Studies Panelists: All Innovation Case-Study Presenters
SESSION 3b: Case-Studies in Gene Editing Governance Co-Chairs: Steffi Friedrichs & David Trus	
12:15 - 12:35	Governance Case-Study 1: <i>Research utilising Genome Editing Technology on Human Embryos (Interim Report: Expert Panel on Bioethics, Council for Science, Technology and Innovation)</i> Speaker: Hidenori Akutsu, Cabinet Office, Japan
	Governance Case-Study 2: <i>UK Policy Experiences of Research involving Gene Editing in Human Embryos</i> Speaker: Ashley Quirke-Tomlins, British Government, UK
12:35 - 12:45	Panel Discussions of Governance Case-Studies Panelists: All Governance Case-Study Presenters
12:45 - 14:00	LUNCH (provided on-site)
SESSION 2b: Setting the Scene – Sectoral Discussions of Gene Editing Applications and Issues Co-Chairs: David Winickoff & Andrew Atkinson	
<i>Each Sectoral Track is led and chaired by a set of experts with the following roles :</i> <i>Role 1: Lead-Speaker</i> <i>Role 2: Commentator 1 (=Chair of the Breakout Discussion)</i> <i>Role 3: Commentator 2 (=Co-Chair of the Breakout Discussion)</i>	
14:00 - 14:30	Applications in Agriculture & Aquaculture Lead-Speaker: Pierre-Benoit Joly, IFRIS and INRA, France Commentator 1/Rapporteur: François Eudes, Agriculture & Agri-Food Canada, Canada Commentator 2: Simon Lillico, The Roslin Institute and R(D)SVS, UK Commentator 3: Anna Wargelius, Institute of Marine Research, Norway
14:30 - 15:00	Environmental Applications Lead-Speaker: Ken Oye, Massachusetts Institute of Technology, USA Commentator 1: Delphine Thizy, Imperial College London, UK Commentator 2: Kevin Esvelt, Massachusetts Institute of Technology, USA Rapporteur: Jason Delborne, North Carolina State University, USA
15:00 - 15:30	Applications in Human Medicine Lead-Speaker: Gary Marchant, Arizona State University, USA Commentator 1: Rolf Zeller, University of Basel, Switzerland Commentator 2 / Rapporteur: Krishanu Saha, University of Wisconsin-Madison, USA Commentator 2 / Rapporteur: Ben Hurlbut, Arizona State University, USA
SESSION 4a: The Big Picture – Panel Discussion Co-Chairs: David Winickoff & Andrew Atkinson	
15:30 - 16:15	Panel Discussion on the Technologies, Applications and Issues of Gene Editing Speakers: all Key-Note Speakers and Sectoral Track Lead-Speakers
16:15 - 16:45	BREAK

TIME			
Plenary Sessions (Location: Banting Theatre)			
SESSION 4b: Smaller Pictures – Sectoral Breakout Discussions of Gene Editing Applications and Issues			
Instructors/Guides: Steffi Friedrichs & Kyle Kierstead			
NOTE: Breakout discussions will be guided by specific questions that need to be addressed; these questions will be developed by the organisers in collaboration with the Sectoral Track Lead-Speakers. Questions will address the following themes: (a) potential benefits and risks, (b) issues of governance, ethics and biosecurity, (c) public engagement, and (d) innovation and commercialisation.			
16:45 – 17:00	Breakout Instructions and Re-location to Breakout Rooms		
	Breakout Group 1 (Room: Banting Theatre)	Breakout Group 2 (Room: Boardroom 306)	Breakout Group 3 (Room: Boardroom 308)
17:00 – 18:00	Breakout Session A: Applications in Agriculture & Aquaculture	Breakout Session B: Environmental Applications	Breakout Session C: Applications in Human Medicine
Plenary Sessions (Location: Banting Theatre)			
18:00 – 18:15	Closure of Day 1		
	Speakers: David Winickoff & Andrew Atkinson		
18:15 – 18:30	Bus transport to Lord Elgin Hotel		
19:30 – 21:00	RECEPTION (networking opportunity with finger food) (Location: Lord Elgin Hotel)

DAY 2: FRIDAY, 30 SEPTEMBER 2016			
TIME			
8:00 – 8:15	Bus Transport to Workshop Venue (for Breakout Session Lead-Speaker, Chair, Co-Chairs and Rapporteurs)		
8:15 – 9:00	Breakout Group 1 (Room: Banting Theatre)	Breakout Group 2 (Room: Boardroom 306)	Breakout Group 3 (Room: Boardroom 308)
	SUGGESTED: Each Breakout Session Lead-Speaker, Chair, Co-Chairs and Rapporteurs ONLY meet to summarise findings of the previous day		
8:30 – 9:00	Bus Transport to Workshop Venue		
... continues from previous day: SESSION 4b: Smaller Pictures – Sectoral Breakout Discussions of Gene Editing Applications and Issues Instructors/Guides: Steffi Friedrichs & Kyle Kierstead			
9:00 – 12:45	Breakout Group 1 (Room: Banting Theatre)	Breakout Group 2 (Room: Boardroom 306)	Breakout Group 3 (Room: Boardroom 308)
	Breakout Session A: Applications in Agriculture & Aquaculture	Breakout Session B: Environmental Applications	Breakout Session C: Applications in Human Medicine
	BREAK (Breakout Sessions decide individually when to take breaks)		
12:45 – 14:00	LUNCH (provided on-site)		
Plenary Sessions (Location: Banting Theatre)			
SESSION 5: Panel Discussion on Innovation Ecosystems for Gene Editing: 'Intellectual Property and Beyond' Co-Chairs: David Winickoff & Laura Victoria Garcia			
14:00 – 14:45	Presentation 1: IPR, Regulation and Realising the Potential of a new Biotechnology Innovation Speaker: David Zilberman, University of California Berkeley, USA		
	Presentation 2: Gene Editing, IP Policy and Scientific Culture: Lessons from Prior Cases Speaker: Robert Cook-Deegan, Duke University, USA		
	Presentation 3: Innovation Pathways and Roadblocks in Genome Editing: Lessons from Biopharma Speaker: Dianne Nichol, University of Tasmania, Australia		
14:45 – 15:15	Panel Discussion on Innovation Ecosystems for Gene Editing Panelists: all Innovation Ecosystems Presenters		

TIME	
Plenary Sessions (Location: Banting Theatre)	
SESSION 4c: Smaller Details of the Big Picture: Reporting from Sectoral Breakout Discussions Co-Chairs: Steffi Friedrichs & David Trus	
<i>NOTE: This session will be organised in terms of themes (i.e. each Session Rapporteur will be asked to report on specific themes, which will then be discussed, in order to avoid that a single theme dominated the discussion); reports will be 7 min per Breakout Session per two themes.</i>	
15:15 – 16:00	Reporting from Breakout Session on (a) potential risks and benefits, and (b) issues of governance, ethics and biosecurity
16:00 – 16:45	Reporting from Breakout Session on (c) public engagement, and (d) commercialisation
16:45 – 17:15	Final Remarks, Next Steps & Meeting Closure Speakers: David Winickoff & Andrew Atkinson
17:15 – 17:45	Bus Transport to Lord Elgin Hotel (transport to airport, etc. upon arrangement)

ANNEX B: Invited Experts and Presenters

- Hidenori Akutsu, Cabinet Office (Japan)
- Nicole Achee, University of Notre Dame (USA)
- Robert Cook-Deegan, Arizona State University (USA)
- Jason Delborne, North Carolina State University (USA)
- Kevin Esvelt, Massachusetts Institute of Technology (USA)
- Francois Eudes, Agriculture and Agri-Food Canada (Canada)
- Greg Gocal, Cibus (USA)
- Perry Hackett, University of Minnesota / Recombinetics (USA)
- Ben Hurlbut, Arizona State University (USA)
- Sheila Jasanoff, Harvard University (USA)
- Pierre-Benoit Joly, National Institute of Agronomic Research (France)
- Fredrik Lanner, Karolinska University (Sweden)
- Simon Lillico, University of Edinburgh / Roslin Institute (United Kingdom)
- Gary Marchant, Arizona State University (USA)
- Dianne Nicol, University of Tasmania (Australia)
- Ken Oye, Massachusetts Institute of Technology (USA)
- Krishanu Saha, University of Wisconsin – Madison (USA)
- Delphine Thizy, Imperial College (United Kingdom)
- Seiichi Toki, National Agriculture and Food Research Organisation (Japan)
- Anna Wargelius-Troedsson, Institute of Marine Research (Norway)
- Rolf Zeller, University of Basel (Switzerland)
- David Zilberman, University of California Berkeley (USA).