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Gene editing for advanced therapies: Governance, policy and society

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Foreword

This report is the result of an Expert Meeting "Gene Editing for Advanced Therapies: Governance, Policy and Society" conducted under the OECD's Working Party on Biotechnology, Nanotechnology and Converging Technologies (BNCT) project on "Open and Responsible Innovation: realising the potential of emerging technologies for health".

Recognising the significance of gene editing for human health, the 1.5-day Expert Meeting discussed governance mechanisms for the responsible use of gene editing in somatic cells for therapeutic purposes. The Expert Meeting was organised under the auspices of the BNCT, hosted by the Federal Ministry of Education and Research (BMBF) in Berlin, Germany, 6-7 July 2017.

The purpose of the Expert Meeting was to explore the core scientific, legal, regulatory and societal challenges facing the responsible development and use of gene editing in somatic cells for advanced therapies, such as regenerative medicine, cell therapy and precision medicine. International stakeholders aimed to identify where new forms of collaboration across science and society may help to promote a reasonable balance of risk and benefit in personalised health and wellbeing.

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Table of contents

Foreword **3**

Key findings and policy messages **5**

1. Introduction **8**

2. Scientific background and therapeutic promise **10**

2.1. Specificity of gene editing 12

3. Governance approaches in an international context **14**

3.1. The primary governance challenges for gene editing and advanced therapies 15
3.2. Promoting public trust: fostering the responsible development of gene editing 17

4. Advancing regulatory science **22**

4.1. Challenges for regulatory science in the field of advanced therapies 22
4.2. Scientific standards 23
4.3. New collaborative models 24

5. Between investment, access to innovation and public health **26**

5.1. Equity and access 26
5.2. Barriers for the uptake of advanced therapies in this field of precision medicine 27
5.3. Reducing upfront costs and lowering potential risks 29

Endnotes **32**

References 33

Figures

Figure 1. Dimensions of “good” governance 19
Figure 2. CRISPR as a platform technology 28

Boxes

Box 1. The California Institute for Regenerative Medicine 30

Key findings and policy messages

Key findings and policy messages from the Expert Meeting:

General

- **A clear technical breakthrough.** Though evidence is still accumulating on the precision of gene editing techniques, CRISPR/Cas9-mediated gene editing is a major technological breakthrough with great potential for advanced cell and gene therapies. To help clarify the issue of off-target effects, a comprehensive and standardised battery of assays for measuring the outcomes of gene editing should be considered.
- **Governance issues similar to other emerging technologies.** Techniques and applications in gene editing are still emerging. Despite the great attention to gene editing in the public sphere, many policy issues in gene editing for advanced cell and gene therapies are also raised in the context of other emerging technologies, e.g., governance must cope with a moving technical frontier and some level of uncertainty around risks and benefits.
- **Degree of public concern distinguishes gene editing.** One potential distinguishing characteristic of gene editing is the degree of public interest and concern. This likely stems from the potential use of the technology not within the current context of somatic therapies, but in the context of human germline modification.
- **Learning from gene editing as a case.** As policies and institutional capacities are developed around the use of gene editing, these could serve as a model for policies in other areas of advanced therapies and emerging technologies for health. Gene editing might afford societies a chance to develop new frameworks for upstream engagement.

Public Engagement

- **Being systematic about public engagement.** The degree of public concern and interest in gene editing underscores the need for public engagement at an early stage in the process of research and development. Engagement processes must be balanced, and stakeholders should be wary of "overselling" the technology. A central lesson of systematic work on public engagement is that openness, transparency and participation are key. It is more appropriate to talk about different "publics" that need to be engaged in different contexts than a single "public".
- **There remains a significant need for developing and sharing successful strategies for integrating public engagement in research and development.** Many countries and stakeholders struggle with putting public engagement into practice, seeking better models for increasing public engagement at an early stage

and integrating findings into policy. Governance frameworks under the rubric of "Responsible Research and Innovation" are seeking to address this issue in a more systematic way by bringing together an array of mechanisms into toolkits and usable resources.

Regulatory Science

- **Effectiveness of existing regulations.** Human somatic cell gene editing technologies are regulated in many jurisdictions. Stakeholders could discuss how effective the existing regulatory regimes are for dealing with current, and future, applications.
- **Meeting challenges for regulatory science.** Many jurisdictions have usable regulatory frameworks for protecting health and ensuring safety of advanced cell and gene therapies. However, the small size of patient pools makes generating the necessary knowledge base quite difficult without extensive institutional cooperation or larger aggregating centres. Some jurisdictions are better set up than others in meeting this challenge. Furthermore, animal models may be less useful in the context of advanced cell and gene therapies than in the testing of pharmaceuticals, placing more emphasis on well-designed clinical trials. More use of post-marketing studies and real-world evidence might offer new approaches.
- **Platform technology.** The regulation of CRISPR might be especially difficult because it is a platform technology that can be employed across multiple fields. Multiple agencies may be charged with setting regulation standards, and levels of societal concern may vary across contexts.
- **Communication between regulators and developers.** Greater communication between the industry/ research community and regulators has the potential to improve clarity in the regulatory process and render the system more efficient and predictable. Guidance documents could help engagement as products near regulatory milestones.
- **Trust and trust-worthiness at the institutional level.** More policy attention could focus on how research institutions build trust and trust-worthiness, including the development of transparent governance with broader participation.
- **Regulatory cooperation.** Discussion around regulatory cooperation among relevant national agencies is ongoing in a number of fora. These discussions should be continued, deepened, and made more inclusive in order to find avenues for facilitating commercialisation and diffusion of therapies across countries.

Innovation and the Public Good

- **Opening innovation.** Identify and analyse possible issues in the existing intellectual property system and discuss options to address possible challenges in the context of health innovation. Future work around open innovation could be built around public research for the public good. Policies should seek to foster collaboration between public and private stakeholders, and between agencies.
- **The goal of public benefit.** Ultimately, the degree of public benefit should be the aim of public policy in this arena, but clear policy choices will not always follow from this mandate. Actors should think beyond just health to a holistic approach that includes the innovation system, increased research leadership, and the just

distribution of benefit. Patients, the broader public, and the innovation system itself are all cited as considerations. As a result, stakeholders should discuss short- and long-term policy options to implement emerging technologies into clinics: how to implement a system of continuous assessment of public health impact along the innovation trajectory; how to realise public benefit of gene editing; what reimbursement models may help the uptake of advanced therapies?

1. Introduction

Recent breakthroughs in gene editing (Cathomen and Keith Joung, 2008[1]; Urnov et al., 2010[2]), and advances in gene editing techniques such as the clustered regularly interspaced short palindromic repeats (CRISPR) system (Doudna and Charpentier, 2014[3]; Jinek et al., 2012[4]) have ushered in a new era for gene editing and health innovation. Deliberate modification of genetic material is of course not new and one could describe gene editing as an "incremental advance in the ability to efficiently manipulate DNA; they change the timelines for, but not the substance of, the ethical debates" (Bubela, Mansour and Nicol, 2017[5]). Research on recombinant DNA (rDNA) molecules and the novel methods employed for such approaches go back to the early 1970s (Jackson, Symons and Berg, 1972[6]; Mertz and Davis, 1972[7]).

When compared to conventional approaches, new gene editing techniques may offer greater precision, lower costs, and more flexibility in their use (National Academies of Sciences, 2016[8]; National Academies of Sciences, 2017[9]; Nuffield Council on Bioethics, 2016[10]). Researchers around the world have been quick to embrace gene editing techniques because of the promise of improved basic research and for better understanding, diagnosing and treating human diseases and conditions (Baltimore et al., 2015[11]; Barrangou et al., 2007[12]; National Academies of Sciences, 2017[9]; Sternberg and Doudna, 2015[13]; Stoddard and Fox, 2016[14]).

A number of promising therapeutic applications of gene editing are already under investigation (Ginn et al., 2013[15]; Kaufmann et al., 2013[16]), with Kane (2017[17]) reporting that the United States (US) Food and Drug Administration (FDA) allowed the first gene editing clinical trials to proceed in 2008. The first human clinical trial using the CRISPR/Cas9 modified cells was approved in the People's Republic of China in 2016 for the treatment of lung cancer (Cyranoski, 2016[18]). Experts anticipate that many more clinical trials employing these methods and tools will commence within the next few years (National Academies of Sciences, 2017[9]).

At the same time, the trajectory of gene editing in research and development and the uptake of future therapies in the clinical setting remain unclear due to uncertainties in the scientific, regulatory, and economic landscapes (see, for example, (Doudna, 2015[19]; The European Group on Ethics in Science and New Technologies (EGE), 2016[20]; Gross, 2016[21]; House of Commons, 2017[22]). These questions can differ depending on, for example, the type of gene editing technology and its application: human or non-human, somatic cell or germline, diagnostic, therapy or enhancement. While each set of questions deserves attention, the focus of the OECD Expert Meeting, and this report, was on human somatic cell gene editing.

Recognising the significance of gene editing for human health, a one and a half day Expert Meeting, "Gene Editing for Advanced Therapies: Governance, Policy and Society", was held in order to discuss governance[1] mechanisms for the responsible use of gene editing in somatic cells for therapeutic purposes. The Expert Meeting was organised under the auspices of the OECD Working Party on Biotechnology, Nanotechnology and

Converging Technologies (BNCT), and was hosted by the Federal Ministry of Education and Research (BMBF) in Berlin, Germany on 6-7 July 2017. Questions focussing specifically on gene editing in the human germline were considered outside the scope of the meeting and this Workshop Report (Baylis, 2017[23]; Bosley et al., 2015[24]; National Academies of Sciences, 2017[9])..

The purpose of the Expert Meeting was to explore the core scientific, legal, regulatory and societal challenges facing the responsible development and use of gene editing for advanced therapies, such as regenerative medicine, cell therapy and precision medicine. International stakeholders aimed to identify where new forms of collaboration across science and society may help to promote a reasonable balance of risk and benefit in personalised health and wellbeing. Current and/ or future barriers to collaboration were also explored.

The desired outcome of the meeting was to increase clarity around current and future innovation trajectories and policy landscape, promoting better understanding, collaboration and alignment amongst stakeholders and jurisdictions.

Objectives of the Expert Meeting were:

1. Pool ideas and approaches from countries for the responsible development of gene editing techniques in advanced and personalised therapies, especially in relation to research policy, ethical, legal and social aspects, regulation, governance and innovation policy.
2. Examine options available to social actors in, and around, public engagement approaches designed to inform governance and regulation.
3. Draw more general policy lessons for the responsible development of emerging technologies.

This report draws directly from, and is informed by, the discussions held over the course of the Expert Meeting. It reports on the key themes articulated by the participants, and sets out their priorities for moving forward. Section 2 provides an introduction to gene editing technology and potential therapeutic applications. Section 3 focuses on the broad governance issues raised by gene editing of human somatic cells for therapeutic applications including ethical, legal and social issues. Section 4 focuses on advancing regulatory science. Section 5 explores the relationship between investment, access to innovation and public health.

2. Scientific background and therapeutic promise

Gene editing aims to modify the genetic sequence at a precise genomic location. Consequently, the treated cells engage in a repair process which may have different outcomes. Gene editing thus depends on the availability of enzymes that can be targeted to any desired genome sequence. The foundations of targeted gene editing were provided by earlier work using zinc finger nucleases (ZFN), transcription activator-like effector nucleases (TALEN), or meganucleases, whose DNA binding domain was engineered to specifically bind each new desired target sequence in the genome. By using these platforms, some potential uses of gene editing for therapeutic applications were explored and brought to the first human testing. More recently, the discovery of the CRISPR/Cas9 system and its application to gene editing techniques in eukaryotes has provided a more versatile and efficient platform.

CRISPR/Cas9 refers to a unique organisation of short, partially palindromic repeated DNA sequences and associated Cas9 enzyme found naturally in the genomes of bacteria and other microorganisms. It offers increased simplicity, flexibility, and, possibly, increased precision in gene targeting, over previous methods (Sander and Joung, 2014[25]). There are however, important health, environmental and ethical concerns that shall need to be addressed prior to clinical use, field trials and environmental release (Oye et al., 2014[26]).

In bacteria CRISPR/Cas9 can mitigate an attack by a viral infection through the destruction of the genome of the invading virus (Brouns et al., 2008[27]; Jinek et al., 2012[4]). By destroying the virus's genome, the CRISPR system can then block the virus from replicating. Each palindromic repeat is followed by short segments of spacer DNA, which are representative of the DNA of viruses that have previously attacked the host (Barrangou et al., 2007[12]; Broad Institute, 2017[28]). In this way the spacers serve as a genetic memory. If another infection by the same virus occurs, the CRISPR defence system will cut any viral DNA sequence matching the spacer sequence and protect the host from the new viral attack; a new spacer is then made and added to the chain of spacer and repeats (Jinek et al., 2012[4]).

CRISPR spacer sequences are copied into short RNA sequences ("CRISPR RNAs" or "crRNA"), which are capable of guiding the system to corresponding sequences of DNA (Broad Institute, 2017[28]). When the target DNA is found, Cas9 – an enzyme produced by the CRISPR system – binds to the DNA and cuts it, blocking off the targeting gene (Doudna and Charpentier, 2014[3]). A research team from Massachusetts Institute of Technology's (MIT) Broad Institute, led by Feng Zhang, building on the work of Doudna and Charpentier, has been able to apply this system to eukaryotic cells (Cong et al., 2013[29]). The implications of CRISPR/Cas9 are significant, as it opens new avenues for research on mammalian cells, including human cells and embryos (Cong et al., 2013[29]).

While there are important questions surrounding the use of gene editing techniques, such as the frequency and the mutations of off-target effects (see Section 2.2 below), its potential is far reaching (Cong et al., 2013[29]). Researchers are currently working towards

using CRISPR/Cas9, and the other gene editing platforms, to target and modify errors in the human genome in order to treat genetic disease (Gross, 2016[21]). However, challenges remain for applying gene editing, including CRISPR/Cas9, to human gene therapy (Fu et al., 2013[30]; Schaefer et al., 2017[31]).

In this vein, National Academies of Sciences, Engineering, and Medicine (2017[9]) has suggested that gene editing applications might be categorised according to four criteria:

- Which cells or tissue(s) are modified, specifically whether modification is made on somatic cells or tissue(s), which are non-hereditary or germ-line, in which changes are passed onto future generations.
- Where the editing takes place, either *ex vivo* or *in vivo*.
- The specific goals of the modification, such as treatment of disease, prevention of disease, or to introduce additional or novel traits.
- The nature of the modification, such as a simple modification of a disease causing mutation or a more complex change.

Significant investment in researching potential products utilising advanced cell and gene therapies have been in development for some time. Recently, the EMA has approved the first cell-based gene therapy (generic product name: strimvelis) in the EU, developed through a collaboration between researchers of the San Raffaele Telethon Institute for Gene Therapy in Milan, Italy, and GlaxoSmithKline (GSK), to treat Adenosine Deaminase Severe Combined Immunodeficiency (ADA-SCID) (Aiuti, Roncarolo and Naldini, 2017[32]). The FDA has approved the first two cell-based gene therapies in the US: two novel chimeric antigen receptor T cell (CAR-T) therapies to treat certain types of leukaemia (generic product name: tisagenlecleucel), and non-Hodgkin lymphoma (generic product name: axicabtagene ciloleucel). Tisagenlecleucel has been developed through a collaboration between the Novartis Pharmaceuticals and researchers from the University of Pennsylvania (Rosenbaum, 2017[33]). These therapies are based on retroviral gene therapy vectors for gene transfer.

There are a number of applications of gene editing, and CRISPR (CRISPR/Cas9) in particular, under development. Researchers have suggested, for example, that the technology may allow clinicians to edit a patient's immune cells to allow for resistance to human immunodeficiency virus (HIV) infection (Lander, 2015[34]; Mock et al., 2015[35]; Tebas et al., 2014[36]). Professor Carl June led a trial in 2014 using zinc-finger nuclease. His group took blood from 12 people with HIV and removed the gene that encodes a protein on T cells that the virus targets, hoping this would prevent infection of the cells. The results were considered to be encouraging (Reardon, 2016[37]). Researchers at UC Berkeley's Innovative Genomics Initiative, under the direction of Dr. Mark DeWitt, have reported some success in correcting the single mutation responsible for sickle-cell anaemia in mice, using CRISPR technology. This research is still in its preliminary phase, with human trials still years away (DeWitt et al., 2016[38]). CRISPR may also prove to be a better option for treating severe combined immunodeficiency (SCID), which is caused by mutations of the Janus family kinase (JAK3) (Chang et al., 2015[39]).

Other examples of the potential application of gene editing for therapeutic purposes are:

- Haemophilia B: a severe haemostasis (the stopping of a flow of blood) disorder due to mutation of the factor IX gene in the X chromosome. CRISPR has been successful in mice to cure haemophilia B, and is thought that similar outcomes can be achieved with humans (Ohmori, Nagao and Mizukami, 2017[40]).

- Leukaemia: leukaemia is a cancer of the bone marrow and blood (white blood cells, red blood cells, and platelets). Genetically modified immune cells (T cells) offer new treatment options in leukaemia and other cancers (Porter et al., 2011[41]; Kaiser, 2016[42]).
- Duchenne muscular dystrophy (DMD): DMD is a genetic disorder categorised by progressive muscle degeneration and weakness. DMD is caused by an absence of dystrophin, a protein that helps keep muscle cells intact. CRISPR offers great promise as a treatment for DMD (Mendell and Rodino-Klapac, 2016[43]).

In parallel with the developments in gene editing, stem cell research, especially the ability to induce pluripotency in somatic cells, has made considerable progress (Yamanaka, 2012[44]). Applying CRISPR technology to human induced pluripotent stem cells (iPSCs) promises researchers the ability to manipulate genes to study their functions in the context of specific disease, or to correct a patient's genetic defect. CRISPR allows researchers to make new control cells for a specific individual that can differ by as little as a single nucleotide making it easier to produce and investigate human cellular disease models with greater speed and effectiveness (Musunuru, 2013[45]).

The following section will briefly examine the target specificity of genetic editing for individual therapeutic purposes, and regenerative medicine and cell therapy.

2.1. Specificity of gene editing

Questions around the specificity of gene editing technologies – i.e., "on-target versus off-target site activity" (National Academies of Sciences, 2016[8]) – have received considerable attention within the scientific literature. In an article, Cho (2013[46]) reported high specificity using the CRISPR system, with no detectable off-target effects (Cho et al., 2014[47]). While Iyer et al. (2015[48]) and Zhang et al. (2015[49]) reported the possibility of some off-target mutations, these previously stated levels were much lower than that reported in a debated correspondence piece published by Schaefer et al. (2017[31]). Since publication of that piece, concerns with respect to its validity have been raised by some members of the scientific community and an addendum has been published by the editors of *Nature Methods* reporting on these concerns.

In the opening talk of the Expert Meeting, "Scenarios of gene editing in research and medicine", Professor Jin-Soo Kim, Director, Center for Genome Engineering Institute for Basic Science and Department of Chemistry, Seoul National University, spoke directly to the issue of off-target activity, the importance of measuring off-target effects, and the validity of claims being made. Professor Kim articulated the need for validation of findings, and spoke to a number of different approaches that have, and are, being developed to measure different outcomes.

Speaking to the need for standardised testing protocols, Professor Kim's words echoed those of Hendel et al. (2015[50]), who have called for "comprehensive and standardised battery of assays for measuring the different gene editing outcomes created at endogenous genomic loci". This would appear to be one area for cross-disciplinary cooperation.

The question of whether off-target effects matter when working with somatic cells was raised during Professor Kim's keynote. Acknowledging the controversial nature of the question, Professor Kim reminded participants that conventional drugs and therapeutic treatments all carry some level of risk to the patient, and pointed to current chemotherapy drugs as a case-in-point. The clinical trials process is used, at least in part, to assess

potential risks to patients. This will be true, too, for clinical trials using gene-editing techniques including the aforementioned HIV trial in which research participants are infused with SB-728-T (Sangamo BioSciences). This trial consists of autologous CD4-enriched T cells that have been modified at the CCR5 gene locus by ZFN (Tebas et al., 2014[36]). As of 2017, the clinical trial was ongoing with over 200 research participants enrolled in the study.

3. Governance approaches in an international context

Gene editing of human somatic cells raises important ethical, legal and societal issues (ELSI), each of which should be considered alongside the development of the technology itself. Many of these questions are not, however, novel; they will instead draw upon the very questions, issues and controversies raised in relation to earlier breakthroughs using gene transfer techniques (such as rDNA) and human gene therapy (see, for example, (Evans, 2002[51]; Frewer and Shepherd, 1995[52]; Habermas, 2003[53]; Swazey, Sorenson and Wong, 1978[54]). As reiterated throughout the meeting by participants, the issues in gene editing themselves are not new and reflective of the challenges in realising the opportunities of emerging technologies and advanced therapies. Rather, the attention derives from the speed and precision offered by today's gene editing methods and tools, and the prospect of potential therapeutic and enhancement applications.

Some types of gene editing applications for health are considered "acceptable" in society today, and others – subject to certain limitations and/ or stringent regulatory safeguards – might be considered "unacceptable" at this time (Baltimore et al., 2015[11]; Naldini, 2015[55]; Lander, 2015[34]). Drawing distinctions between interventions aimed at therapy versus enhancement, as well as the distinction between somatic and germline, help clarify typical ethical and legal distinction between acceptability and unacceptability. The former is commonly noted to include somatic cell gene editing for therapeutic purposes, while the latter is commonly noted to include germline editing for either therapeutic or enhancement purposes. The framework also provides a basis to begin to think about the appropriate governance frameworks (e.g. regulation) that may be appropriate to oversee gene editing technologies and tools (Nicol et al., 2017[56]). It is important to note that while it is possible in practice to separate somatic from germline human gene editing, the boundary between somatic and germline cells is not 100% impermeable in principle.

Questions around how to govern advances in genetic engineering at the national and international level have been a fundamental component of the broader biotechnology dialogue since the earliest experiments on rDNA took place. They have been intimately entwined with the scientific advances, as illustrated by the voluntary guidelines that came out of the 1975 Asilomar Conference on Recombinant DNA, which were instrumental in shaping the relevant governance framework (Berg et al., 1975[57]; Berg and Paul, 2008[58]; Fredrickson, 2001[59]).

As such, while recent advances with CRISPR are raising a multitude of questions that will need to be addressed by stakeholders, as noted above, many of these questions will not be new in themselves. Moreover, relevant stakeholders will have the benefit of learning from earlier advances in genetic engineering, as well as other emerging technologies (such as, for example, nanotechnologies (Macnaghten, Kearnes and Wynne, 2005[60]; Stilgoe, 2007[61]).

Section 3 of the report examines what governance challenges may arise for, and around, gene editing for advanced therapeutics and asks what, if anything, is novel here. Identifying potential major governance challenges early in the development and

commercialisation of the technology and associated products may help to avoid unnecessary and/or inappropriate, regulatory and legal hurdles.

3.1. The primary governance challenges for gene editing and advanced therapies

One area that demands considerable attention now, and in an on-going fashion is governance. In particular, this includes the methods, tools employed (i.e., the gene editing process itself), and the end products created through the technology including, for example, specific cell therapies based on gene-edited somatic cells.

Regulatory frameworks suitable to govern human gene editing, including somatic cell editing, currently exist in numerous jurisdictions, and within the international arena (Knoppers et al., 2017[62]; National Academies of Sciences, 2017[9]). For example, FDA representatives (Ritu Nalubola and Denise Gavin) noted ongoing activities in the U.S., including overarching U.S. government initiative to modernise the federal regulatory system for biotechnology products (United States Executive Office of the President, 2016[63]; United States Executive Office of the President, 2017[64]) as well as FDA's proactive efforts to ensure the safety of products while also facilitating innovation in this area. FDA has a well-established programme, regulating human medical products that apply genome editing to exert their therapeutic effect under its existing framework for biological products, which include gene therapy products. FDA's interactions with domestic and international regulatory partners are illustrative of regulatory cooperation among relevant agencies, and the importance of such collaboration for effective and efficient regulation.

While not designed specifically for this next generation of methods and tools, they will, by default rather than design, be captured by the current laws and regulations. Stokes (2012[65]) has coined this process as a form of "inherited regulation". With reference to existing regulatory frameworks Abou-El-Enein et al. (2017[66]) point to technology-based safety and efficacy issues in the development and use of gene editing for novel therapies.

The questions that need to be answered, therefore, are not whether human somatic cell gene editing technologies are regulated – as they are in many jurisdictions – but rather how effective the existing regulatory regimes are for dealing with current, and future, applications. "Effectiveness" must, however, also be viewed through a framework that takes into account regulatory pluralism, cultural and political norms, and broader societal values. This potentially gives rise to tensions when considering cross-jurisdictions issues, especially within the context of regulatory and policy coordination.

For some participants, "effectiveness" here means everything from transparency in decision-making processes within the laboratory through to the relevant regulatory agency; increasing efficiencies in policy development; and ensuring an adequate scientific evidence base for regulatory decision-making (Nicol et al., 2017[56]). At the same time, an effective regulatory approach must ensure the safety and efficacy of advanced cell and gene therapies for individuals – including in utero treatment of the foetus (McClain and Flake, 2016[67]) – and provide relevant agencies with adequate powers to enforce the regulations.

In this section of the report, we identify the key themes and associated challenges of governing gene editing technologies, and set out the potential policy implications thereof.

3.1.1. Legal Lag or the Pacing Problem

One of the challenges of any new technology is the "the pacing problem". Marchant (2011[68]) describes this issue as the "inability of legal and regulatory frameworks to keep pace with technologies" due to their rapid emergence into the marketplace (Charo, 2015[69]; Wallach, 2015[70]). The US National Academies has recently recommended that "existing regulatory infrastructure and processes for reviewing and evaluating somatic gene therapy to treat or prevent disease and disability should be used to evaluate somatic gene therapy that uses gene editing" (National Academies of Sciences, 2017[9]).

In order to minimise the amount of regulatory lag at the national level, and in relation to broader governance frameworks that exist at the international level, there was support among participants to begin the process of ensuring that regulatory frameworks will continue to be able to address evolving applications. Regulatory agencies present at the meeting noted the adequacy of existing frameworks under which human medical products obtained through these technologies are covered.

3.1.2. Better regulatory coordination across borders

It was suggested that more regulatory coordination across jurisdictions, and between regulatory agencies and industry and research institutes, may increase regulatory efficiency. It was also suggested that jurisdictions with larger regulatory agencies and greater capacity than their international counterparts, might create platforms for the collective sharing of information. This could include technical data (not covered by confidentiality clauses), as well as information on public engagement activities and educational information about the regulatory process. Such efforts could build on, and supplement, existing international forums in which information sharing and capacity building is critical. These include, for example, International Pharmaceutical Regulators Forum (IPRF)[2] and the Asia Partnership Conference of Pharmaceutical Associations (APAC)[3] Forum.

Participants advocated for greater engagement between regulatory agencies and those actively creating the products that they regulate. Working with, and making available guidance documents, to industry and research community as products near regulatory milestones, has the potential to improve clarity in the regulatory process and build efficiency and predictability into the system.

3.1.3. "Leakage", misuse and misleading claims

Once a therapy has been approved for use by the relevant regulatory body, the potential exists that the therapy can be used for purposes other than which it was approved (so-called "leakage" and/or misuse). Participants pointed to the field of stem cell science when talking about the potential misuse of promising treatments, as well as the potential for misleading claims and misplaced hype associated with new therapeutic application (Bianco et al., 2013[71]; Bubela, Mansour and Nicol, 2017[5]; Levine and Wolf, 2012[72]). These concerns, as they relate to cell based regenerative medicine, have been summarised by Caulfield & McGuire (2012[73]) as follows: "despite this clinical reality, unproven stem cell therapies are being marketed to patients in some regions and countries. The clinics that offer these services operate outside of ethical or regulatory oversight and exploit individuals at their most vulnerable by offering unproven treatments for incurable and debilitating diseases".

Limited regulatory powers over stem cell clinics and the therapies they market in some jurisdictions would appear to have provided clinics and clinicians with an environment in which misuse and misleading claims may be made. Bubela et al. (2017[5]) propose healthcare leaders to stay informed about evidence based research, take a neutral position (avoiding positive and negative hype), and to be involved in international debates.

3.2. Promoting public trust: fostering the responsible development of gene editing

3.2.1. The public engagement challenge

Running across the two days of meetings were questions and themes around public engagement in the governance of gene editing research and development. When, how and why should stakeholders engage with the public on gene editing? How can engagement be done effectively? What are the potential impacts of public engagement on policy agendas and governance? A recent report by the Genetic Alliance UK (2017[74]) aims to help scientists communicate on this topic in an accessible way. The report points out the importance of the consistent use of terminology in public engagement.

Advances in gene editing techniques promise to deliver new and novel ways for treating disease and disability, with – as set out in Section 2 – a number of clinical trials are currently ongoing and novel therapies are reaching the market. Because of the high investments associated with R&D activities that underpin these advances, the potentially high access costs of future treatments, and the blurring distinction between therapeutic use and enhancement, participants articulated a need for governments and other relevant stakeholders, to engage with publics on gene editing technologies at this early stage of development. Meaningful engagement, it was stated, is one way to build trust and trust in institutions, including research institutions, as the technology and its products begin to mature. Moreover, governments and policy makers should create ways in which publics may participate in the development of the broader governance landscape in a meaningful, on-going and transparent way (Wilsdon and Willis, 2004[75]; Macnaghten, Kearnes and Wynne, 2005[60]).

The EU's pharmacovigilance legislation enables the Pharmacovigilance Risk Assessment Committee (PRAC) to hold public hearings during certain safety reviews of medicines. They support the committee's decision-making by providing perspectives, knowledge and insights into the way medicines are used. Key objectives and benefits are to: 1) increase transparency by opening up the scientific evaluation process; 2) empower EU citizens by giving them a voice in the evaluation of the safety of medicines; 3) improve the public's understanding of the scientific and regulatory processes; 4) add value to the evaluation process beyond existing channels of stakeholder engagement. Public hearings are open to all members of the public and offer a tool allowing the European Medicines Agency (EMA) to engage with European Union (EU) citizens in the supervision of medicines and listen to their views and experiences. The hearings[4]:

- Contribute to EMA's knowledge of how the public and patients perceive the use of certain medicines.
- Help EMA understand the possible results of its recommendations on the safe use of medicines.
- Present the public with another means to provide input into EMA's decision-making.
- Help the public understand EMA's evaluation of a medicine's safety.

In this vein Nicol et al. (2017[56]) argue that a global, cross-sector discussion will important to further advance CRISPR-mediated somatic cell therapy towards clinical use. Given the diverse ethical, social, medical, and commercial questions raised by gene editing for advanced therapies, a wider engagement of all stakeholders, including the publics, would help regulatory decision making. While there appeared to be consensus among participants at the Expert Meeting in Berlin that there is no one "right" mechanism for public engagement (Rowe and Frewer, 2005[76]), participants did point to examples of what they considered to be "best practice" for engagement. They included, for example, the Danish Consensus Conference Model, which has been utilised by stakeholders across varying topics and jurisdictions (Einsiedel, Jelsøe and Breck, 2001[77]; Grundahl, 1995[78]). It was further suggested by Mr. Simon Burall, Programme Director, Sciencewise, that there was much that could be learnt from the ways in which public engagement had been successfully employed – or not – in the case of earlier technologies including, for example, genetically modified foods, nanotechnologies and mitochondrial donation (Barber and Border, 2015[79]; Gaskell et al., 1999[80]; Macnaghten, Kearnes and Wynne, 2005[60]; Wilsdon and Willis, 2004[75]). This sentiment was echoed by Dr. Lars Kluver, Managing Director, Danish Board of Technology Foundation, Copenhagen, who also noted that the tool-box for public engagement activities already exist. Where it needs to be refined and improved is, in his view, with online public engagement approaches.

3.2.2. The importance of building trust and trustworthiness in institutions

In his keynote, "Responsible governance for gene editing for health innovation", Professor Peter Dabrock, Chair, Depart of Theology, Friedrich-Alexander Universität Erlangen-Nürnberg, reminded meeting participants of the importance of trust and trustworthiness in institutions, especially when dealing with highly complex and technical scientific applications such as gene editing. As illustrated by the public backlash against, for example, genetically modified foods in the EU (Bauer and Gaskell, 2002[81]; Gaskell et al., 1999[80]; Pollack and Shaffer, 2009[82]), acceptance of technologies, and their products, by the consumers, cannot be taken for granted.

In order to avoid such scandals in the future, Professor Dabrock suggested that there is an onus on relevant stakeholders to actively, and continuously, engage with the public and to do so in a way that fosters trust in the institutions that govern the technologies or play an oversight role in the development of the technology. The framework provided by Responsible Research and Innovation (RRI) provides one approach for thinking about how to build trust and the types of issues and concerns that may be raised by publics in relation to advances in gene editing. It also provides a myriad of tools for doing so. For Professor Dabrock, the way to build "sustainable trust regimes – Or: …build trust in institutions", is by embracing the four dimensions of "Good" Governance, as illustrated by Figure 1 below.

Figure 1. Dimensions of "good" governance

Source: Prof. Dr. Peter Dabrock, Dr. Matthias Braun; Friedrich-Alexander-Universität Erlangen-Nürnberg, Germany, Presentation at Expert Meeting, BMBF, Berlin, Germany (6 July 2017).

In this way, building trust and trust in institutions is more than a question of the robustness of currently regulatory regimes, their operation and enforcement. Rather, it is about building legitimacy in the broader governance framework with different publics, at different points in time, while, at the same time, actively managing expectations. In this vein Gardner et al. (2017[83]) suggest the positioning of emerging regenerative medicine products in "development spaces" to support their characterisation, deliberation, and positioning in anticipation of their adoption in a clinical settings.

3.2.3. Engaging the "publics"

Public acceptance of gene editing technologies, and the products that they give rise to will be influenced by a range of factors, including the distribution of benefits provided by these new treatments. Participants articulated a need for a diversity of viewpoints to be heard in public engagement activities so as to ensure that no one group or agenda dominated the public discourse. The U.S. National Academies has recently recommended that "transparent and inclusive public policy debates should precede any consideration of whether to authorise clinical trials of somatic cell gene editing for indications that go beyond treatment or prevention of disease or disability" (National Academies of Sciences, 2017[9]).

The idea of opening up technical debates goes beyond just the constituency represented in the discussions, but also to the framing of the issues. Sarewitz (2015[84]) has, for example, argued that public discourse, including public engagement activities, dealing with science and technology issues need to go beyond the narrow risk framing traditionally employed by the scientific community. By exposing policy makers to the richness of the debates, they may better embrace the complexities and do so in a way that is more meaningful and transparent, and better reflect the values of their constituency. This is especially true if done early on in the technology's development.

This in turn helps build trust and public acceptance. Such sentiments are echoed by Jasanoff, Hurlbut, & Saha (2015[85]), who has reminded us that: "Limiting early deliberation to narrowly technical constructions of risk permits science to define the

harms and benefits of interest, leaving little opportunity for publics to deliberate on which imaginations need widening, and which patterns of winning and losing must be brought into view".

Given the nascent nature of gene editing at this time, policy makers and other relevant stakeholders have a somewhat unique opportunity to actively embrace public engagement activities, and inform policy development, as the technology itself matures and reaches the market. This may, in turn, help to build trust between the public and key stakeholders.

As discussed by participants, a significant barrier for researchers who wish to engage with the public on the topic of their work is the nature of public funding initiatives. Schemes that fund basic science and/or translational research often do not incentivise public engagement activities. As such, researchers who are often best placed to talk about the nature, scope and potential impact(s) of their work with the public are provided with limited opportunities, where they even exist, in doing so.

Independent entities/ organisations, including those within the scientific community, should be encouraged to participate in engagement activities. Their active involvement may assist in building trust in the institutions and the science. Stakeholders should be encouraged to engage with the publics around gene editing now, using a variety of engagement tools that current exist, and refining where necessary. Funding bodies should be encouraged to incentivise public engagement by members of the scientific community with the publics. Also, the development of best practices around engaging journalists and the media at large would assist in building knowledge.

3.2.4. Areas for international cooperation

A plurality of regulatory arrangements that apply to gene editing research and project development already exist across jurisdictions, suggesting that close convergence of these schemes is highly unlikely. While this may present some challenges for regulatory coordination, opportunities will exist for jurisdiction to collaborate and aim for coordination on a number of other areas including, for example, development of best practice protocols, tools and guidance documents, along with capacity-building of individuals, research programmes and regulatory agencies more generally.

Other areas that may benefit from international cooperation, and should be explored, include the standards development (see Section 4.2 below), creation of cross-jurisdictional infrastructure for clinical trials and public funding of research programmes.

In order to accelerate the process of providing accurate, efficient gene editing therapies for patients around the world, participants articulated a need to rethink the current approach for clinical trials. It has long been recognised that clinical trials are resource intensive – time and money – adding significant costs to bringing a new product to market. Target diseases identified for novel CRISPR-based therapies are present in the minority of the population. This has implications for study recruitment, including the rate at which patients are entered into studies, and the duration of the studies, which may act as a barrier to bring novel therapeutic treatments into the market in a timely way.

Given that enrolments in clinical trials tend to be low, building a better cross-jurisdictional infrastructure for clinical trials was discussed. For meeting participants, the creation of a permanent, but flexible, infrastructure that worked to speed up the trials process, while not sacrificing safety and efficacy data collection required by regulators, could provide meaningful benefits – including critical mass – to the innovation process.

Patient organisations as well as rare disease networks (e.g. Orphanet, EURORDIS) may play a role here.

Some participants noted the potential need to review and analyse how this type of research is funded. In particular, several participants articulated a need for public funding agencies to incentivise research collaborations across jurisdictions. The rationale for this, as discussed by participants, was to strengthen the global research ecosystem so as to accelerate the rate at which new therapies and applications can make it to the market.

Inherent in this call is the need to minimise, wherever possible, duplication across research endeavour and focus on streamlining research efforts that address the most pressing needs. Some governments, it was acknowledged, may be reluctant to engage in cross-jurisdictional funding models due to the concerns over loss of, for example, competitive advantage, intellectual property (IPs) and confidentiality issues. While these may be barriers, they should not be seen as insurmountable obstacles. The research and translational medicine collaboration between Novartis Pharmaceuticals and the University of Pennsylvania for developing a novel, personalised CAR-T immunotherapy offers an example of new kinds of business models (Diller, 2012[86]).

4. Advancing regulatory science

The rapid evolution of complex research tools, technology, and therapies presents a growing set of challenges for regulatory agencies and the development of regulatory science (Food and Drug Administration, 2011[87]; Nicol et al., 2017[56]). The specific challenges of regulatory science in the context of gene editing must be viewed in this context. Robust regulatory policies are necessary and, indeed critical, to ensuring the timely commercialisation of therapeutic products while, at the same time, addressing safety and effectiveness concerns (Hamburg, 2012[88]; Kurz, 2017[89]).

International coordination concerning regulatory science could help maximising the potential benefits of gene editing technologies, while also minimising the risks. Creating systems of reciprocity for learning and sharing information in real time will, it was suggested, support translating data into knowledge. Central to this collaboration shall be the respect for autonomy, sharing of best practices, and open communication, all of which shall provide the basis for a strong and ethical framework. Earlier international engagement, it was thought, might simplify the relationship of science and society downstream.

A number of challenges about regulatory science were posed by the experts. While there was some agreement that further standardisation of regulatory science in the field might be warranted, it was also pointed out that efforts to do so were ongoing in some international and national fora.

4.1. Challenges for regulatory science in the field of advanced therapies

There are a number of challenges facing regulatory science in the field of advancing technology. Notably, many of the concerns are not new in and of themselves, but new technologies, such as CRISPR change their scope and scale (Nicol et al., 2017[56]). Many of the primary concerns will be centred on the pre-clinical to clinical transition, most notably through the uncertainty around the risk benefit dynamics of new technologies. A number of key issues were raised, including:

- Hype around the technology. Caution needs to be exercised in talking about CRISPR and the types of therapies that might emerge. The use of the technology in advanced therapies remains, for the most part, in the pre-clinical R&D phase. Much more research is needed, given what scientists know and do not know about the human genome.
- Standardising and improving tests for off target effects (see Section 2.2 above): “what are the acceptable levels of off-target effects” and “who decides”?
- Safety will be difficult to assess at the onset of clinical trials. As such, there is a real risk that trials could be halted prematurely or allowed to continue putting patients at risk.

- Because CRISPR is a platform technology that can be employed across multiple fields, regulation and managing societal unease might be especially difficult. Multiple agencies may be charged with setting regulation standards.
- CRISPR also enables researchers to both delete and/ or insert genetic information. The question was, therefore raised, as to whether the different modes should be regulated differently.
- Finally, participants noted that gene editing for therapeutic purposes shares a blurry line with enhancement. How will, it was posed, regulators deal with human enhancement? And, further, how will individual country's transgressions—if they can even be considered that—be dealt with in the absence of an international framework? Such questions all point to the need for an ongoing multi-lateral dialogue, especially around the development of a flexible governance framework.

4.2. Scientific standards

Better standardisation and validation of gene editing tools will be imperative for accelerating innovation, and for promoting safety. There is, as noted by one participant, to develop numerous standards, including both physical and non-physical standards. In regards to the former, it was noted that standards are needed e.g. for assays, end-points, efficacy and potency. Non-physical standards are needed around, e.g. international learning and sharing, clinical trials, and enforcement of guidelines (that are both appropriate and achievable). While it was suggested that the proliferation of standards was a good development, this statement was countered by the concern that there are real risks associated with overlapping standards. Thus, it was argued that there is a need to create, now, cohesive systems to deal with overlapping standards and to share best practice tools.

There are already bodies well placed to do this, including the OECD, the International Organization for Standardization (ISO), the WHO Expert Committee on Biological Standardization, the Comité Européen de Normalisation (CEN), and the International Alliance for Biological Standardisation (IABS). ISO is a multi-jurisdictions standards developing body, with extensive reach (Kica and Bowman, 2012[90]). While ISO has not, at least to date, created a Technical Committee (TC) specifically for gene editing, ISO/TC276-Biotechnology was established in 2013. The scope of TC276 includes the following: terms and definitions; biobanks and bio-resources; analytical methods; bioprocessing; data processing including annotation, analysis, validation, comparability and integration; metrology (ISO, 2017). Given the breath of TC276's work programme, it appears likely that their work will include the development of some standards that are applicable to gene editing technologies.

In addition to the landscape of international standard setting bodies, many jurisdictions have national and/or supranational standards setting bodies, which often feeds into the ISO system. These include, for example, Standards Australia, the Canadian General Standards Board (CGSB), Korean Agency for Technology and Standards (KATS), and the South African Bureau of Standards (SABS).

One of the US standards setting bodies, the National Institute of Standards and Technology (NIST) announced in mid-2017 the creation of a Genome editing Consortium (National Institute of Standards and Technology (NIST),(n.d.)[91]). The Consortium aims to promote coordination between NIST and stakeholders within the gene editing community to advance standards for genome editing technology. Additionally, the

Consortium will partner with the newly formed Standards Coordinating Body (SCB), which aims to "advance process, measurement, and analytical techniques to support the global availability go regenerative medicine products and services" (Body, 2017[92]).

There are also important standards emanating from professional societies. International Society for Stem Cell Research (ISSCR)[5] is an independent, non-profit organisation aimed to "promote and foster the exchange and dissemination of information" as related to stem cells, to encourage research around stem cells, and to promote education in all areas of research and application of stem cells". With a membership base of more than 4,000, drawn from over 60 countries, the organisation appears well positioned to promote cross-disciplinary collaboration on fronts, including standards development on gene-editing related stem cell research and commercialisation.

4.3. New collaborative models

Kenneth Taymor, Deputy Director of the Forum for Collaborative Research and Executive Director Centre at UC Berkeley School of Public Health, suggests the regulator's role as the gate keeper will need to evolve. Traditionally, there has been a single pathway leading to clinical trials. In his presentation, he suggested that gene editing provides, arguably, an opportunity to re-think this approach.

Taymor articulated one potential model that would utilise working groups for the purposes of identifying particular scientific issues. The working groups would bring stakeholders together in order to discuss how to address issues based on data. Members of the working group would voluntarily disclose relevant data to their counterparts within the working group. This, Professor Taymor suggested, would promote a more collaborative approach; one that would accelerate data generation and innovation. This would be particularly helpful in quickly mitigating off-target effects, which is a lingering concern.

Some participants pointed to the recent report released by the U.S. National Academies of Science. *Human Gene Editing: Science, Ethics and Governance* (NAS, 2017). This report set out principles that should be considered for regulatory guidance. Namely, that gene editing technologies should promote well-being, have transparency, practice due care, remain a responsible science, offer respect for persons, and foster fairness (National Academies of Sciences, 2017[9]). These principles provide a background for discussions on how gene editing is controlled within fundamental laboratory research, somatic cell gene editing for treatment or prevention of disease and disability, and heritable gene editing. Recommendations for regulatory science are offered in each of these arenas.

The NAS (2017[9]) report recommends that the use of gene editing as a laboratory research tool in human somatic cells and tissues would likely follow the regulatory pathways and ethical norms already established for other types of laboratory research. These practices include somatic cells, the donation and use of human gametes (and progenitors) and embryos for research process – where this research is permissible. However, it should be noted that significant divergence already exists between jurisdictions in terms of how these activities are regulated.

When considering somatic cell gene editing, NAS (2017[9]) noted that there is public support for the use of gene therapy for treatment and prevention of disease and disability. As such, clinical trials for somatic cell gene editing are beginning worldwide. However, the report has recommendation that authorities should, for the time being, authorise clinical trials or approve gene therapies only for indication related to disease or disability.

Furthermore, the report counsels that "Oversight authorities should evaluate the safety and efficacy of proposed human somatic cell genome-editing applications in the context of the risks and benefits of intended use, recognising that off-target events may vary with the platform technology, cell type, target genomic location, and other factors".

5. Between investment, access to innovation and public health

The third and final session of the Expert Meeting explored options to balance robust innovation policies, fair and equitable access to new products, and health system sustainability in the context of gene editing for advanced health therapies. Within science and technology policy there is need for a deeper understanding of the investment mechanisms, collaboration frameworks, data and IPRs policies – including cross-licensing agreements, patent pools and open source – which can support innovation and equitable access to technology.

In recent years, new models of "open science" and "open innovation" organised around hubs, accelerators and centres of excellence have begun to address some of these barriers including, for example, high upfront costs, investment risks, fragmented policy, and a lack of standards (or delayed standard setting). Experimenting with these new models of investment, along with development of other models, may offer stakeholders opportunities to accelerate innovation within this field.

This section of the report examines potential pathways for maximising return on investment with R&D activities while, at the same time, promoting greater access to the products developed through these programmes.

5.1. Equity and access

Advances with gene editing technologies and tools appear likely to produce novel treatments for a number of diseases and conditions for which there have been very few, if any, effective therapeutic options. Professor Bartha Maria Knoppers, Centre of Genomics and Policy, McGill University, Montreal, QC, Canada, noted that Article 15 of the International Covenant on Economic, Social and Cultural Rights (ICESCR), requires States to recognise the right of everyone to enjoy the benefits of scientific progress and its applications. This right according to the UNESCO Venice Statement of 2009 includes the need to:

- conserve, develop, and diffuse science
- respect the freedom indispensable for scientific research
- recognise the benefits of international contacts and co-operation in the scientific field.

Professor Charis Thompson, Center for Science, Technology, and Medicine in Society, UC Berkeley, USA, noted that, while biomedical uses of human gene editing will need to maintain an individualist point of view that puts the doctor-patient relationship at its centre, it is vital not to lose track of societal level impacts of these technologies (Thompson, 2017[93]). Policy makers must be equipped to measure such impacts, and have meaningful representation to mitigate those impacts deemed undesirable by those especially affected, and by the public more generally.

As Professor Tania Bubela, Dean and Professor, Faculty of Health Sciences, Simon Fraser University, Canada, stated in her keynote presentation, "Can CRISPR Advance Public Health? Responsible Management of Clinical R&D IP", the same advances may reduce the costs associated with producing a range of conventional therapies that are prohibitively expensive by bringing down, for example, costs associated with cell processing and manufacturing. Should this be true, Professor Bubela stressed the need for finding ways that promote access so that the therapies "are not developed by the 2% for the 1%", that is, by the wealthiest countries for only the wealthy within those countries.

Inherent in this comment, and as discussed by participants over the course of the meeting, is the need to examine the reimbursement models utilised by governments and the private sector, as access is intrinsically coupled to willingness to pay. In this sense, reimbursement models may operate as one of the most significant barriers for the uptake of advanced therapies in the short to medium term as governments and other entities seek to calculate the individual and population health benefits generated by the technology.

5.2. Barriers for the uptake of advanced therapies in this field of precision medicine

Innovation policies and structures, including the IPRs architecture, will also need evaluation. Divergences in how jurisdictions define patentable subject matter around human genetic materials and the subsequent granting (or not granting) of rights, has been widely discussed (Pottage, 1998[94]; Sampat and Williams, 2015[95]). These discussions appear likely to be exacerbated with new gene editing methods and tools (Nuffield Council on Bioethics, 2016[10]). With CRISPR technologies still in the pre-competitive R&D space, an opportunity exists, as articulated by Professor Bubela, to look to alternative financing and IP models that can help to accelerate the commercialisation of therapies, while bringing down cost.

In her keynote, Professor Bubela cautioned against the granting of patents over the platform technology itself and patents in the pre-competitive R&D space that have overly broad claims/ fields of use. The granting of patents with overly broad fields of use, she noted, occurred early on with gene technologies, resulting in the technology being locked down. Actors were subsequently pushed out of the pre-competitive R&D space, and the creation of a path dependency environment for the technology quickly occurred. This, she cautioned, needs to be avoided with CRISPR.

Such barriers have, however, begun to emerge with the United States Patent Trademark Office (USPTO) awarding a broad patent for CRISPR gene editing technologies to MIT's Broad Institute (US Patent 8, 679, 359). The award was unsuccessfully challenged by Professors Doudna and Charpentier and the University of California Berkley (UCB) (The Broad Institute, Inc. v. The Regents of the University of California, Patent Interference No. 106, 048, DK) (see, for example, (Cohen, 2017[96]; Ledford, 2016[97]). In contrast to the decision of the US Patent Trial and Appeal Board, on 23 March 2017, the European Patent Office announced its intention to award a broad patent for CRISPR gene editing technology to Doudna/ UCB, the University of Vienna, and Professor Charpentier (Umeå University). The differing patent decisions for CRISPR technologies in the two jurisdictions will likely produce more complicated licensing agreements. However, as noted by Nicol et al. (2017[56]), license agreements offer the potential to manage ethical and legal issues and to increase social benefits (Nicol et al., 2017[56]).

Scholars such as Contreras and Sherkow (2017[98]), two leading IPRs experts, have argued that those who control CRISPR patents should "open up larger swaths of the

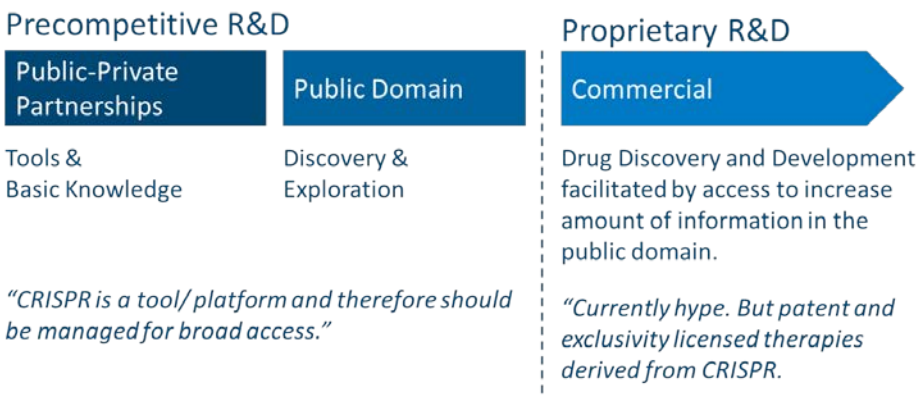
genome to beneficial commercial research" and embrace "more flexible licensing approach[es]". Such an approach would help, in their view, minimise the patent bottlenecks that have already started to appear as a result of the narrow licensing agreements. They go on to argue that this would foster innovation, especially within the field of human therapeutics (Contreras and Sherkow, 2017[98]; Contreras and Sherkow, 2017[99]). Horn (2017[100]), however, has countered this proposal, suggesting instead that patent pools "would provide a more competitive and effective solution".

Finding solutions that incentivise innovation, while still rewarding the patent holder, will be fundamental to bringing new genetic therapies into the market in a timely manner. Cook-Deegan, in contrast, has advocated for a cross-licensing deal (see (Cohen, 2017[96]). In this type of deal, an agreement is reached to grant a license to each other for the development of the subject matter claimed in one or more of the patents each owns.

Public-private partnerships (PPPs) and the use of CRISPR as a platform technology have been identified as a potential model when markets are atypical and for avoiding lock-down of IPRs, and promoting broad access to patents created during the pre-competitive R&D phase (Barker, 2016[101]; Bubela et al., 2017[102]; OECD, 2015[103]). PPPs, as summarised by Professor Bubela, are "collaborative efforts to achieve mutually agreed objectives…that draw on the respective strengths and resources of the parties involved..." Benefits of multiparty PPPs in the pre-competitive R&D space include free flow of information and know-how between partners (see Figure 2). Given the complexity of some novel therapeutic approaches (i.e. cellular immunotherapy in cancer) health innovation may benefit from the involvement of manufacturers (e.g. bioengineers specialised in cell processing, manipulation, sorting, and expansion to clinical dosage levels) (Bubela et al., 2017[102]) This could facilitate both research, innovation and commercialisation within this early R&D space. Here the TB structural genomics consortium is an example of successful PPPs in the health innovation (Williamson, 2000[104]; Celia W. Goulding et al., 2002[105]).

Despite the potential benefits offered by the PPP model, it was noted that the most common relationship currently being utilised is the "hub and spoke model" under which "a central party enters into bi-lateral research agreements with multiple parties to advance its centralised goal".

Figure 2. CRISPR as a platform technology



Source: Prof. Dr. Tania Bubela, Faculty of Health Sciences, Simon Fraser University, Canada, Presentation at Expert Meeting, BMBF, Berlin, Germany (6 July 2017).

Some participants pointed out the need for stakeholders to investigate the full array of relationship models, and do so in such a way as to allow for experimentation across the different R&D phases. Participants also stressed need for institutions, especially universities, to rethink their technology transfer models so as to ensure that their IP portfolios are managed in such a way as it is in the best interest of the public. This would include, for example, avoiding – wherever possible – exclusive licensing deals during the pre-clinical R&D phase.

5.3. Reducing upfront costs and lowering potential risks

The high resource needs associated with R&D activities, manufacturing and bringing new therapeutic products onto the market is widely acknowledged (Adams and Brantner, 2006[106]; Morgan et al., 2011[107]), and is often used to justify high prices and the patent protections afforded to the pharmaceutical industry (Glass, 2004[108]; Trouiller et al., 2002[109]). While the former is discussed to limit access to treatment, the latter may stifle innovation. Advancements in complementary and foundational technologies such as bioinformatics and whole genome sequencing are critical components that will directly impact the costs of gene editing therapies.

In addition to exploring options for cross-jurisdictional R&D programmes that are funded by multiple entities, including governments (see Section 4 above), there are lessons to be learned from earlier, non-traditional, enterprises and activities that have been successful in addressing scientific, organisational, regulatory and economic barriers to research and health innovation. These include, for example, The California Institute for Regenerative Medicine (CIRM; see Box 1), which was established and funded through the sale of USD 3 billion in state bonds. The approach taken with the CIRM funding and governance model illustrates that governments may fund large-scale research and development programmes through non-traditional funding models, through which they may receive a benefit – financial and/ or other – from the funded enterprise.

Box 1. The California Institute for Regenerative Medicine

The history of stem cell funding in California may hold lessons relevant to issues raised by gene editing for advanced therapies. The California Institute for Regenerative Medicine (CIRM)[6] was established as a result of the successful passage of Proposition 71 (Prop 71), the California Stem Cell Research and Cures Act (the Act), on 2 November 2004. Codified as Article XXXV of the California's Constitution, the Act authorised USD 3 billion for stem cell research over a ten-year period and created CIRM "to support stem cell research…for the development of life-saving regenerative medical treatments and cures" (SEC 2). An oversight body, the Independent Citizens Oversight Committee (ICOC), was also established through the passage of the Act. In addition to establishing standards for research and intellectual property rights, a key function of the 29 member ICOC was to represent the public—patients, researchers and industry—in grant and award decisions and those relating to CIRM operations. It is important to note that the funding and research mandate of the CIRM including "all stem cells", and was not focused specifically on one type of stem cell (i.e., embryonic stem cells).

Despite its altruistic mission—"the development of life-saving regenerative medical treatments and cures" (CIRM, 2016[110]) – the CIRM has been the subject of significant controversy. In their review of the CIRM, Adelson and Wienberg (2010[111]) note that the CIRM has had to respond to concerns relating to public funds benefitting the corporate sector, transparency in funds distribution, its policy on intellectual property (IP), real and/or perceived conflicts of interest (CoI) of the ICOC members, and return-on-investment. The authors note that such criticism has "come from sources opposed not to stem cell research itself but rather to other aspects of the endeavour" (Adelson and Weinberg, 2010[111]). In response, the CIRM put into place clear research priorities, and policies that addressed CoI and IP issues. Despite the "difficult beginning" (2010[111]), Adelson and Weinberg conclude that the CIRM "as a major center for stem cell research" and has "taken on a vigorous life of its own".

Prop 71 can be seen as a tool that accelerated stem cell research within CA and the US more generally. As of 2016, the CIRM had filed over 180 patents, initiated 27 clinical trials and funded over 750 projects. However, no products have come to market. According to the CIRM's President, Dr. Randal Mills, "cures and treatments [can now be seen] on the horizon for some of the most vexing challenges in medicine" (CIRM, 2016[110]). With the initial tranche of funds due to run out by 2020, CIRM's direction is not yet clear. One option would be to seek additional public funds through a second ballot measure.

Longaker et al. (2007[112]) sought to assess the return on investment of Prop 71 and, by extension, the CIRM for the state of California. Framing their analysis of Prop 71 by "assessing the net advantage to society", authors suggested than any evaluation needed to consider a range of metrics including economic impact of the research itself, the health benefits accrued to society, net spending on healthcare, opportunity costs and economic growth for California more generally. This, they went on to acknowledge, is "not straightforward" (Longaker, Baker and Greely, 2007[112]), and could only be conducted some years out from its establishment. Such conclusions apply equally to the types of therapeutic applications that are likely to be generated through gene editing technologies.

The need to explore R&D funding models such as that embraced by the state of California, and other alternatives, was articulated by meeting participants across the two days. While some of these discussions dealt specifically with the need for new business models around patents, and IPRs more generally (including, as noted above, PPPs), participants also identified a range of approaches that may reduce costs and potential risks for patients. They included:

- Encouraging cross-jurisdictional funding models for basic R&D activities.
- Promoting greater coordination across jurisdictions in terms of clinical trials so as to minimise duplication of efforts.
- Encouraging multi-jurisdictional studies, that bring small pockets of patients from across the globe under one clinical trial umbrella (see Section 4, above).
- Establishing a global repository for best practice guidance and tools.
- Promoting greater coordination on reporting requirements for clinical trials (including adverse outcomes), and requirements around informed consent.

In this regard Professor Knoppers, re-emphasised the right of citizens to benefit from science and the potential harm to health systems due to the non-use of data. The following three changing contexts in open science could help build a more systemic and pragmatic approach in open science for the public good:

- Strengthening infrastructure science and participation of citizens for more sustainable health care systems (e.g. bioinformatics, biobanks, and data-bases that are accessible by researchers, health care specialists, citizens…).
- Establishing a proportionality approach in ethics review that measures real risks and real benefits – moving away from the presumption that research is per se harmful (e.g. implementing the use of ethics approved broad consent; mutual recognition between ethics committees).
- Moving from closed data silos to data sharing in order to deliver more sustainable health care systems.

Each approach raises questions relating to, for example, data protection, cross-jurisdictional data sharing, confidentiality, and consent. These complex issues should not, it was suggested, be used as barriers to exploring different models and approaches but rather as the justification for encouraging a diversity of stakeholders to be active participants in investigating the different options and applications.

Endnotes

[1] Governance is the exercise of political, economic and administrative authority necessary to manage a nation's affairs. https://stats.oecd.org/glossary/index.htm

[2] https://www.i-p-r-f.org/index.php/en/

[3] http://apac-asia.com/

[4] http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2017/06/WC500229781.pdf

[5] http://www.isscr.org/

[6] https://www.cirm.ca.gov/

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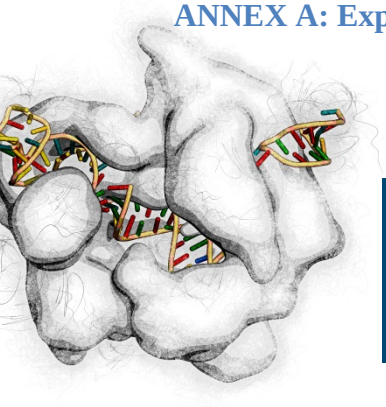
ANNEX A: Expert Meeting Agenda



Gene editing for advanced therapies governance, policy, and society

OECD Expert Meeting
6-7 July 2017, Berlin, Germany

Scope

The 1.5-day expert meeting "Gene editing for advanced therapies: governance, policy, and society" will discuss governance mechanisms for the responsible use of gene editing in somatic cells for the purpose of promoting human health. The expert meeting is organised under the auspices of the OECD Working Party on Biotechnology, Nanotechnology and Converging Technologies (BNCT). It will be hosted by the Federal Ministry of Education and Research (BMBF) in Berlin, Germany.

Gene editing using CRISPR/Cas9 and comparable methods offers great promise for better understanding, diagnosing and treating diseases and conditions. A number of promising applications are already entering research and therapy. At the same time, the trajectory of these disruptive tools and their uptake in the clinic remain unclear due to uncertainties in the scientific, regulatory, and economic landscapes. Policy makers, researchers and the public are confronted with new regulatory, ethical and social questions around the development and implementation of gene editing technologies and applications. Implications of gene editing in the human germline are discussed in other fora and will not be in the scope of this meeting.

The purpose of the expert meeting is to explore the core scientific, legal, regulatory and societal challenges facing the responsible development and use of gene editing in somatic cells for advanced therapies, such as regenerative medicine, cell therapy, and precision medicine. International stakeholders will aim to identify where new forms of collaboration across science and society may help to promote a reasonable balance of risk and benefit in personalised health and well-being.

The desired outcome of the expert meeting is to increase clarity around current and future innovation trajectories, promoting better policy, understanding, collaboration and alignment amongst stakeholders and countries.

Objectives

1. Pool ideas and approaches from countries for the responsible development of gene editing technologies in advanced and personalised therapies, especially in relation to research policy, ethical, legal and social aspects, regulation and governance, and innovation policy.
2. Examine options available to social actors in, and around, public engagement approaches designed to inform governance and regulation.
3. Draw more general policy lessons for the responsible development of emerging technologies.

Day One; 6 July 2017

9:00-9:15 **Welcome messages**

Dr. Stephan Roesler (Deputy Director, Ethics and Law in the Life Sciences, BMBF, Germany)

Prof. Dr. Francesc Gòdia (Professor of Chemical Engineering, Autonomous University of Barcelona, Barcelona, Spain)

Dr. David Winickoff (Senior Policy Analyst, Secretary of Working Party on Bio-, Nano- and Converging Technologies (BNCT), OECD, Paris, France)

Moderation: **Dr. Mark Bale** (Deputy Director, Science Research and Evidence Directorate, Department of Health, UK)

9:15-9:40 **Opening talk: Scenarios of gene editing in research and medicine**

Prof. Dr. Jin-Soo Kim (Director and Professor, Center for Genome Engineering, Institute for Basic Science and Department of Chemistry, Seoul National University, Seoul, South Korea)

The opening talk will present a scientific overview of the scientific, regulatory and social trajectories of gene editing in research and clinical use. Opportunities, possible applications and challenges of CRISPR/Cas9 and targeted gene editing technologies in medicine. Future scenarios for how these new techniques will engage the field of advanced and personalised therapies.

9:40-10:05 **Keynote: Responsible governance of gene editing for health innovation**

Prof. Dr. Peter Dabrock (Chair, Department of Theology, Friedrich-Alexander-Universität Erlangen-Nürnberg, Germany)

This keynote will highlight societal trajectories of gene editing for health innovation. Ethical, legal and social tensions that policymakers and regulators need to balance. Potential pathways for realising the greatest social value.

10:05-13:00 **Session 1**

Governance approaches in an international context

Session moderator: **Dr. Lyric Jorgenson** (National Institutes of Health (NIH), Deputy Director, Office of the Director, Office of Science Policy, Bethesda, USA)

Gene editing techniques raise challenges for how current systems of governance – regulation, rules and soft law – ought to shape this emerging field. This session attempts to map recent national and international developments in the governance of gene editing for advanced therapies, e.g. regenerative medicine, cell therapy, precision medicine. Experts from different national contexts will discuss existing and future approaches to law, regulation, innovation policy and stakeholder engagement; what are the mechanisms for meaningful public input into regulatory and policy-making processes?

Key policy questions to be discussed:

1. What are the primary governance challenges in the arena of gene editing and advanced therapies across different regulatory systems? For example, assessing risk and benefit;

distinguishing therapy and enhancement; research versus clinical use.

2. What kinds of government decision-making practices garner public trust and foster the responsible development and use of gene editing technologies for therapeutic applications?
3. Where might international cooperation on these challenges help?

Comments:

- **Prof. Paolo Gasparini** (Direttore, Genetica Medica, Direttore del Dipartimento, Dipartimento dei Servizi e di Diagnostica avanzata, IRCCS, Trieste, Italy)
- **Dr. Denise Gavin** (Chief, Gene Therapy Branch, Division of Cellular and Gene Therapy, Office of Tissues and Advanced Therapies, Center for Biologics Evaluation and Research, FDA, HHS, USA)
- **Dr. Srinivasan Kellathur** (Head, Advanced Therapy Products, Premarketing, Health Science Authority, Health Products Regulation Group, Singapore)
- **Dr. Debra Mathews** (Assistant Director for Science Programs, Johns Hopkins Berman Institute of Bioethics; Associate Professor, Department of Pediatrics, Johns Hopkins University School of Medicine, Baltimore, MD, USA)
- **Dr. Ritu Nalubola** (Senior Policy Advisor, Office of Policy, Office of the Commissioner, FDA, USA)
- **Dr. Martina Schüßler-Lenz** (Chair, Committee for Advanced Therapies CAT, European Medicines Agency; Deputy Head, Section Advanced Therapy Medicinal Products, Paul-Ehrlich Institute (PEI), Langen, Germany)

Group work and panel discussion:

- **Mr. Simon Burall** (Programme Director, Sciencewise, UK)
- **Dr. Heidi Howard** (Senior Researcher, Centre for Research Ethics & Bioethics (CRB), Uppsala University, Sweden)
- **Prof. Dr. Christof von Kalle** (Managing Director, NCT Heidelberg, Professor and Chair Translational Oncology, National Center for Tumor Diseases Heidelberg (NCT), Germany; Head Translational Oncology, German Cancer Research Center Heidelberg (DKFZ), Germany)
- **Professor Glyn Stacey** (UK Stem Cell Bank Director, National Institute for Biological Standards and Control (NIBSC), UK)
- **Prof. Dr. Andrew Webster** (Professor, Director SATSU, Department of Sociology, University of York Heslington, York, UK)
- **Prof. Dr. Christiane Woopen** (ceres - Cologne Center for Ethics, Rights, Economics, and Social Sciences of Health; University of Cologne, Germany)

13:00-14:00	**Lunch break**
14:00-15:00	**Session 1 (cont.)** **Governance approaches in an international context**
15:00-15:30	**Coffee break**

15:30-17:30

Session 2
Advancing regulatory science

Session moderator: **Dr. Ubaka Ogbogu** (Assistant Professor, Faculty of Law and Faculty of Pharmacy and Pharmaceutical Sciences, University of Alberta, Edmonton, Canada)

This session addresses issues of regulatory science in the field of gene editing for advanced therapies. It does so against the backdrop of growing challenges to regulatory agencies in the face of a rapid evolution of complex research tools and therapies. Participants will discuss how different regulatory systems are coping with fast-moving technological change in gene editing and advanced therapies. There is uncertainty among the public, policy makers, and the regulatory agencies about the actions required.
Key policy questions to be discussed:

1. What are the main challenges for regulatory science in the field of advanced therapies, especially for those using gene editing?
2. How to stimulate the development, standardisation, and validation of gene editing tools in advanced therapies to assess safety and effectiveness?
3. How might collaborative, international efforts be helpful in developing robust approaches to regulatory science?
4. What are the potential benefits and pitfalls of using emerging forms of Artificial Intelligence (AI) systems in (pre-)clinical testing (e.g. to better understand off target effects)? What could be the process of integration and who develops the standards? Are there unique liability issues?

Comments & panel discussion:

- **Prof. Dr. Toni Cathomen** (Professor of Cell and Gene Therapy Center for Chronic Immunodeficiency at Center for Translational Cell Research, Director Institute for Cell and Gene Therapy, Medical Center, University of Freiburg, Germany)
- **Dr. Hervé Chneiweiss** (Directeur, Neuroscience Paris Seine, CNRS, Inserm/ Université Pierre et Marie Curie, Paris, France)
- **Prof. Dr. Maria Cristina Galli** (Department of Cell Biology and Neurosciences, Istituto Superiore di Sanità Roma, Italy)
- **Dr. Sol Ruiz** (Head of Division, Biologics and Biotechnology, Spanish Agency of Medicines and Medical Devices, Madrid, Spain)
- **Prof. Dr. Kenneth S. Taymor** (Deputy Director, Forum for Collaborative Research, UC Berkeley School of Public Health, USA)

17:30-18:30

Reception

Day Two; 7 July 2017

Moderation: **Dr. David Winickoff** (Senior Policy Analyst, Secretary of Working Party on Bio-, Nano- and Converging Technologies (BNCT), OECD, Paris, France)

9:00-9:25 **Keynote**

Open and responsible innovation – collaborative forms of research and product development

Prof. Dr. Tania Bubela (Professor, School of Public Health, University of Alberta, Canada)

This keynote will assess the current innovation landscape for the development of novel therapies using gene editing techniques, and help locate collective norms or approaches that may be useful from the perspective of public health goals.

9:25-12:45 **Session 3**

Between investment, access to innovation and public health

Session moderator: **Prof. Dr. Charis Thompson** (Chancellor's Professor, Center for Science, Technology, and Medicine in Society, UC Berkeley, Berkeley, USA; Professor, Department of Sociology, London School of Economics and Political Science, London, UK)

This session explores options to balance robust innovation, access, and health system sustainability in the context of gene editing for advanced health therapies. Within science and technology policy there is need for a deeper understanding of the investment mechanisms, collaboration, data and intellectual property (IP) policies that can support both innovation and equitable access to technology. In recent years, new models of "open science" and "open innovation" organised around hubs and centres of excellence have been one way to address high upfront costs, investment risks, fragmented policy, and lack of standards. The session will draw on real-world case studies in which policy actors engage the innovation process upstream through incentives and IP structures to minimise trade-offs between the rate of innovation and cost.

Key policy questions to be discussed:

1. What are the biggest barriers for the uptake of gene editing technologies and advanced therapies?
2. How is public benefit assessed and what will ensure the just distribution of benefits?
3. What are options and mechanisms to share and reduce upfront R&D costs (e.g. licensing rules, open science) across sectors?

Comments:

- **Dr. Lars Klüver** (Managing Director, Danish Board of Technology Foundation, Copenhagen, Denmark)
- **Prof. Dr. Bartha Maria Knoppers** (Full Professor and Director of the Centre of Genomics and Policy, Faculty of Medicine, Human Genetics, McGill University, Montreal, Canada)

- **Dr. Roli Mathur** (National Centre for Diseases Informatics & Research (NCDIR), Bengaluru, India)
- **Dr. Gunnar Sandberg** (Vinnova – Swedish Governmental Agency for Innovation Systems, Sweden)

Group work and panel discussion:

- **Dr. Richard Johnson** (BIAC, CEO, Global Helix LLC and member, National Academy of Sciences Board on Life Sciences, USA)
- **Prof. Dr. Won Bok Lee** (Professor, Ewha Womans University Law School, Seoul, Korea)
- **Ms. Katherine Littler** (Senior Policy Advisor, Wellcome Trust, UK)
- **Prof. Dr. Luigi Naldini** (Professor, Cell and Tissue Biology and Professor of Gene and Cell Therapy, "Vita Salute San Raffaele" University School of Medicine, Milan, Italy)
- **Dr. Françoise Roure** (Présidente de la section Sécurité et Risques, Ministère de l'Économie et des Finances, Paris, France)
- **Assistant Professor Dr. Krishanu Saha** (Assistant Professor, Biomedical Engineering, BIONATES, Madison, USA)

12:45-13:00	**Summary & conclusions**
13:00	**End of meeting**