FEAM
Federation of European Academies of Medicine

Human Genome Editing in the EU

Report of a workshop held on 28th April 2016 at the French Academy of Medicine

The Academy of Medical Sciences

Académie Nationale de Médecine

With the financial support of the Interacademy Partnership for Health and the Foundation of the Academy of Medicine

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Executive Summary

The meeting was jointly organised by the Federation of European Academies of Medicine (FEAM), the UK Academy of Medical Sciences and the French Academy of Medicine, France. It was supported by the InterAcademy Partnership for Health and the French Academy of Medicine Foundation (FAM). The aim of the meeting was to consider the landscape for human genome editing across the EU (and associated countries, including Switzerland) and to:

- Understand current scientific activities in the EU with respect to genome editing, focusing on human applications.
- Understand the current regulatory landscape for human genome editing research and clinical applications, across the EU.
- Understand the ongoing societal and political debates on genome editing across the EU and within the relevant agencies of the European Commission.
- Identify any areas where there were significant differences between the countries and, if possible; consider the driving forces for these differences (e.g. ethics, public opinion)
- Discuss the need for a European regulatory framework to govern the safe and acceptable use of human genome editing.

In seeking to deliver these objectives, it was intended that the workshop could help foster discussion between experts to promote best practice, and to consider whether common European guidelines might be developed. The workshop focussed on three key aspects of genome editing:

- The current opportunities for and the regulation of genome editing for use in early research.
- Clinical research and the applications of genome editing in human somatic cells.
- Clinical research and applications in human germline cells.

A very wide range of issues were covered at the workshop. Although it had not been possible for a formal consensus to be sought, the need for the development of a positive and well-publicised statement on the potential benefits of genome editing, was supported in general.

Delegates at the workshop were optimistic regarding the development of an EU-wide consensus on the benefits of and the further development of the clinical use of genome editing in somatic cells. The need and benefits of constantly updating the regulatory guidance in this area was now seen as a priority. The preparation of such regulatory guidance would require ongoing effective dialogue between regulators and researchers – not only from the academic sector, but also drawing on the extensive experience of the commercial sector.

Genome editing research using germline cells and/or embryos was considered important by many participants and necessary not only to inform basic research about human development, but also to improve the efficacy and safety of genome editing techniques to better support a potential future use in clinical settings.

The divergent views held at the national level across individual EU Member States on the acceptability of such research, particularly where the use of embryos is involved, was identified as a key barrier to the provision of research funding by the European Commission (via Horizon 2020). However, even if the position of the European Commission in setting up

such a major barrier to the provision of such research funding was unlikely to change at present, many participants indicated a wish for this restriction to be softened.

Although they are starting to be resolved quite rapidly, safety and efficacy concerns, in addition to the long-established ethical considerations referred to above, do remain major barriers to the introduction of clinical applications of genome editing in germline cells and embryos. At the same time, a counter-argument continues to be made that it would be unethical not to use genome editing if it could lead to a reduction in disease and suffering.

> The real need for increased engagement of patients and wider society in general in order to promote a better understanding of the future potential benefits of genome editing was acknowledged. Linked to this was the need to develop a shared language (including common definitions) which could help those in different countries better understand the application of the science of genome editing and the different positions and opinions being developed etc.
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> For example, the definition of an "embryo" is somewhat different across Europe. There were frequent references at the meeting to the recognition that many countries' regulations are outdated as they predate the technological advances that underpin the re-emergence of the associated ethical discussions.

The scientific content of the workshop was overseen by a FEAM Scientific Steering Committee, co-chaired by Professor Pierre Jouannet: nominated by the French Academy of Medicine (French Academy of Medicine) and Dr Robin Lovell-Badge: nominated by the UK Academy of Medical Sciences (Group Leader and Head of the Division of Stem Cell Biology and Developmental Biology, the Francis Crick Institute, London), and which was coordinated by Ms Catherine Luckin (Head of International Policy, UK Academy of Medical Sciences). The other members of the Scientific Steering Committee were:

- Professor Luigi Naldini (Director of the Division of Regenerative Medicine, Stem Cells and Gene Therapy, San Raffaele Scientific Institute, Italy)
- Professor Virginijus Šikšnys: nominated by the Lithuanian Academy of Sciences (Biotechnology Institute, Vilnius University, Lithuania)
- Professor Ernst-Ludwig Winnacker: nominated by the German National Academy of Sciences Leopoldina (Ludwigs-Maximilians-Universität München, Genzentrum, Germany)
- Professor Miika Vikkula: nominated by the French speaking Belgian Royal Academy of Medicine (Professor of Human Genetics, Laboratory of Human Molecular Genetics, Catholic University of Louvain, Belgium)

Approximately 100 delegates (registrants listed in Appendix 2) from across Europe, the United States and elsewhere attended the workshop, a number of which also took part in the public meeting on genome editing which was held the following day by the Study Committee of the US National Academy of Science and US National Academy of Medicine.

The conference report was written by Dr Jeffrey Kipling (Science Policy Adviser, FEAM) and who accepts responsibility for all errors of omission and commission.

Welcome and introductory statements

Welcoming comments: Professor Pierre Jouannet (French Academy of Medicine)

Professor Jouannet welcomed delegates to the meeting and to the home of France's National Academy of Medicine. He reminded participants that the concept of genome editing is not a recent development. The new CRISPR/Cas-9 technology and similar approaches to genome editing, which are more easily available, and far cheaper, are pushing the limits in their use. He referred to some of the more recent global developments in research in the field (with particular reference to China) and how such studies had stimulated increased dialogue within the scientific community on whether there was a need for additional regulatory oversight.

Professor Jouannet explained that the FEAM workshop had been organised to review the landscape for human genome editing research (and its governance) across the EU, and to identify whether anything could be done to support further research in the field.
He reminded delegates of the two publications, reviewing the current state of EU regulations and debate, which had been prepared in advance of the meeting by the UK Academy of Medical Sciences[1] and the French National Academy of Medicine[2].

Introductory comments: Professor Bernard Charpentier (President, FEAM)

Professor Charpentier gave an overview on the role and objectives of FEAM - the Federation of European Academies of Medicine. FEAM is made up of 18 National Academies of Medicine and has access to more than 5000 of the leading biomedical scientists and clinicians in Europe. With its independence from vested interest, and with a commitment to the promotion of excellence in science, FEAM's mission is to provide independent scientific advice within the EU on human and animal medicine, biomedical research, education and health. Some of its current policy priorities included; EU legislation affecting biomedical research (particularly in the use of health data), precision medicine, the development of the "One Health " concept, the culture of prevention in health and the longer-term future of health research.

Recognising that co-operation was essential for the development of effective science policy advice, FEAM was pleased to have observer status at IAMP – the global network of medical academies. At the European level it had a number of formal collaborative arrangements in place with other scientific federations, including acatech, ALLEA, EASAC and Euro-Case. FEAM also participated in various stakeholder coalitions and joint activities across Europe in topics such as data protection and the use of animals in research. Professor Charpentier thanked the French Academy of Medicine for hosting the event, and together with the UK Academy of Medical Sciences, for its work in organising the workshop. He thanked Dr Robin Lovell-Badge, Professor Jouannet and Catherine Luckin (UK Academy of Medical Sciences) for arranging the programme. He gave particular thanks to the InterAcademy Partnership for Health (IAP) and the French Academy of Medicine Foundation (FAM) without whose financial support the meeting could not have taken place.

[1] http://www.acmedsci.ac.uk/policy/policy-projects/genome-editing

[2] http://www.academie-medecine.fr/wp-content/uploads/2016/05/report-genome-editing-ANM-2.pdf

Session 1: Establishing the EU context

Chair: Professor Bernard Charpentier (President, FEAM)

The perspective of the European Commission: Dr Charles Kessler (Principal Scientific Officer, DG Research & Innovation)

The Innovation Chain

Dr Kessler gave an overview of the "innovation chain" from basic research to (potential) clinical application of some aspects of genome editing, and how this research field is influenced by current EU regulations, which are in turn influenced by Member State legislation.

Dr Kessler began by providing some context to the extent of the Horizon 2020 (H2020) EC budget for research, within which funding for the "Excellent Science" programme was €24.4 billion, which for the "Industrial Leadership" initiatives was €17.0 billion, and that for supporting "Societal Challenges" projects was €29.7 billion. Within the Societal Challenges programme some €7.4billion was spent on Health, Demographic Change and Well-being.

Health research funding is widely spread throughout H2020 and provides funding opportunities for many different communities and purposes including loans for small and large R&I companies, the support of public-private partnerships with pharmaceutical companies, collaborative projects in general, public-public partnerships with EU Member States and beyond, basic blue-sky research, training programmes and support for the knowledge triangle.

The current main objectives of the Health Research programmes were to ensure:

- Better health for all
- A more competitive European health industry and care sector
- Maximising the digital potential
- Addressing health as a global challenge

Turning to the specific issue of human germline gene modification in Europe, Dr Kessler noted that the EU does not have any formal competence to determine what research in this field may or not be carried out in individual Member States. There were, at the time of the meeting, national bans on such research (particularly that involving embryos) in 16 Member States, with most countries also having signed up to the Oviedo Convention and its restrictions on the conduct of certain types of research.

Delegates were reminded that Article 13 of the Convention stated that: *"An intervention seeking to modify the human genome may only be undertaken for preventive, diagnostic or therapeutic purposes, and only if its aim is not to introduce any modification in the genome of any descendants."*

Dr Kessler explained that Article 19 (which addresses ethical principles) of the H2020 regulations, states that a number of fields of research cannot be financed by the EU. These include:

- Research activity aimed at human cloning for reproductive purposes.
- Research activity intended to modify the genetic heritage of human beings which could make such changes heritable (except for cancer treatment of the gonads).
- Research activities intended to create human embryos solely for the purposes of research or for the purpose of stem cell procurement, including by means of somatic cell nuclear transfer.

Whilst research involving embryos is permitted in a number of Member States (and in some countries, like the UK, this includes the creation of embryos), the EC has agreed not to support research that leads to the destruction of embryos.

A number of research programmes of relevance to genome editing are however supported by the EU under H2020 (and previously by the 7th Framework Programme). These include:

- ATECT - Advanced T-cell Engineering for Cancer
- CARAT- Chimeric Antigen Receptors for Advanced Therapies
- SCIDNET- Developing genetic medicines for severe combined immunodeficiency (SCID)
- COSYN- Co-morbidity and synapse biology in clinically overlapping psychiatric disorders.

Other fields of EU-funded genome editing relevant research include:

- Functional genomics and disease modelling
- Developmental biology
- Immunology
- Rare disease research
- Xenotransplantation
- Plant disease resistance and plant breeding
- Improved tools and techniques
- Social science research

Turning to the regulatory oversight of genome editing (research and potential products) in the EU, Dr Kessler identified a number of relevant EC Directives and Regulations. These included:

a. *Directive 2004/23/EC on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells.*

This Directive applies to tissues and cells, including bone-marrow stem cells, reproductive cells, foetal tissues and cells, and adult and embryonic stem cells. It applies only to cells and tissues applied to the human body, but not *in vitro* research or animal models. It was not considered that the Directive would interfere with decisions made by Member States concerning the use or non-use of any specific type of human cells, including germ cells and embryonic stem cells.

b. *Regulation (EC) No 1394/2007 on Advanced Therapy Medicinal Products*

This Regulation focuses on gene therapy, cell therapy and tissue engineering. It sets up the centralised marketing authorisation procedure for the EU, including the establishment of the specialised assessment committee (the EMA's CAT). To date, there had only been one gene therapy product on the market, but with another expected shortly.

c. *Directive 2001/20/EC on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of Good Clinical Practice in the conduct of clinical trials on medicinal products for human use (Art.9 para. 6)*

and

d. *Regulation (EU) No 536/2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC (Art.90)*

Under this Regulation, no gene therapy clinical trial may be carried out which deliberately results in modifications to the subject's germline genetic identity.

In summarising the current research and regulatory landscape for genome editing research, Dr Kessler re-stated the Commission's position, and that EU-funded human germline genome editing research was not possible. By contrast, somatic cell genome editing was moving ahead and was being encouraged via H2020 funds, in fields such as disease modelling, functional genomics, development of research tools, as well as ongoing support for gene therapy studies. Knowledge was evolving; many challenges remained, particularly in overcoming some of the lack of clarity in this field in the public's understanding. Genome editing did not equate to the development of "designer babies".

Session 1: General Discussion

Dr Kessler's comment in his presentation that the many challenges remaining meant that the door had to be kept open for science was welcomed.

A comment from a delegate suggested that the scope of the prohibitions (regarding some aspects of research and clinical activity in human germline genome editing) within the Oviedo Convention may be less clear than is usually assumed. Delegates were also reminded that the statement made in December 2015 by the Council of Europe Bioethics Committee asserted Article 13 as a starting point for public discussion (read with Art 28) and not as the last word.

In this context it was also been noted that Article 13 of the Convention was actually written to deal with somatic gene therapy more than germline genetic alteration.

A number of queries were raised throughout the Workshop that sought clarification on the EC's restrictions on supporting research on human germline editing, and whether this covered just clinical applications or all research activity on the germline modification? It was questioned whether embryos acquired from donors from IVF programmes needed to be under the scope of the research prohibition? It was argued that these embryos actually hadn't been created for research purposes, and would be destroyed anyway if no longer required for a specific parental project. In response, Dr Kessler pointed out that as those IVF-derived embryos, which were not implanted, would need to be destroyed, some Member States did not allow their use in research, and so the Commission was not able therefore to provide research funding for such studies.

In response to a related question on whether current EU opposition to supporting research on the human germline could be changed, Dr Kessler suggested that whilst political circumstances (and public opinion) across the EU may change in time, it was not likely that the current restrictions on funding within H2020 would be amended. Many EU Member States continued to be strongly opposed to certain aspects of human genome editing and the use of embryos in research.

It was noted that much of the current research carried out in the EU on genome editing was

actually funded by individual Member States, and by the EC via H2020. This led to some delegates to suggest that there could be opportunities for some supportive national funding agencies to work together on preparatory pilot studies in advance of some possible future changes to EU-wide funding restrictions.

The topic was discussed again later in the meeting, but some delegates raised at this point whether it was timely for the development of a better definition of what constituted a clinical trial in the context of human genome editing, and what really constituted a “first time in man study” in this context? It was suggested, in response, that all such matters remained opened to interpretation.

There was interest over the possible restriction of movement of scientists across the EU (and elsewhere) as a result of current restrictions on genome-editing editing research. It was noted that there were no EU-level restrictions in place, but individual Member States may take a position on the matter. It was suggested in this context that a German scientist, working on embryos outside the country, possibly could be prosecuted under German legislation. If the Head of a laboratory in Germany sent one of his/her laboratory staff members to another country to pursue such work, then it was possible that the lab head could also be prosecuted. It was further speculated that such researchers would find it hard, if not impossible to find further research funding, in any field, upon their return to Germany.

In the context of recent changes to legislation in the UK on mitochondrial replacement as a clinical application, it was suggested to Dr Kessler that as an embryo couldn’t be classed as a “medicinal product” under EU Clinical Trial regulations, it was currently unclear as to what was the situation for germline editing? In response, Dr Kessler suggested that this would need to be down to the individual Member States to decide.

Session 2: Research-current state, opportunities and regulation

This session had been developed to explore the current state of genome editing, the future opportunities afforded by such techniques, and any regulation governing their use within the context of basic research.

The session began with some introductory remarks from the session Chair, before a keynote presentation which provided an introduction to the science of genome editing. This was followed by a panel session where panel members, representing a range of different countries, each provided five minutes of introductory remarks before engaging in wider discussion with all delegates.

Chair: Professor Virginijus Šikšnys (Vilnius University)

In his opening comments, Professor Šikšnys gave a brief overview of the earlier work (2011-2012) that he and colleagues at Vilnius University had carried out on the CRISPR-Cas9 system. This work had included the cloning of the entire CRISPR-Cas locus from *S.thermophilus* and its expression in *E.coli*, which had enabled it to be demonstrated that CRISPR systems were self-contained units. Further biochemical studies had led them to characterise Cas9's mode of action. They had also been able to direct Cas9 to chosen target sites.

An introduction to the science of genome editing and it's portential use in research and medicine: Dr Robin Lovell-Badge (The Francis Crick Institute, London)

Dr Lovell-Badge started his overview of the science of genome editing by reflecting on why there was such a high level of interest in this area of research, globally, at this time. He explained that many techniques, in some way relevant to modern genome editing techniques such as CRISPR-Cas9, have been developed over the years including; transgenic mice, IVF, gene targeting via homologous recombination in ES cells, PGD, the cloning of mammals, the development of human ES cells and iPS cells. Common routes to germline genetic alteration have included:

- Treatment by chemical or ionising radiation to give germline mutations.
- The injection of DNA into the pronucleus of fertilised eggs to give "transgenics".
- Genetic manipulation of embryonic stem cells (ES) which are then introduced into early embryos to give chimeras, which can pass on the genetic change to their offspring.
- Genetic manipulation of somatic cells in culture, followed by nuclear transfer into enucleated eggs and their subsequent development to produce "cloned" animals carrying the genetic change.
- Genetic manipulation of spermatagonial stem cells in culture, followed by their re-introduction into testes (pre-treated to make infertile), where they will give rise to functional sperm.
- Use of genome editing, notably CRISP/Cas-9 techniques, in fertilised eggs, ES cells, somatic cells or spermatagonial stem cells.

With each new method developed, the same ethical concerns over "eugenics" and "designer babies" had arisen, and each time it had been argued that that the technology was either too inefficient or too unsafe to use in humans. Dr Lovell-Badge argued however that the situation had changed significantly through the increased knowledge of genes, genomes and genomic variation, and through the development of more precise and efficient means of

altering DNA sequences provided by genome editing methods – from ZFNs to TALENs and now with CRISP-Cas9.

The ability to develop transgenic mice through pronuclear injection was developed over 30 years ago, and this technique had been used to obtain or assess gene expression. Whilst being a very valuable tool for researchers, it is unreliable, inefficient and can lead to mutations. Since then other transgenic animals (rabbits, sheep and cows) have been developed. Further progress was subsequently made in the development of mouse embryonic stem cells, chimeras and germline transmission. Other groups developed new ways to alter almost any specific DNA sequence in the mouse genome by homologous recombination in ES cells and the production of genetically altered mice. Again- whilst this has been very valuable in the development of cell lines and animal models, it was a somewhat inefficient process.

The creation of "Dolly", the sheep, through somatic cell nuclear transfer (SCNT) demonstrated that genetically modified animals could be derived from perhaps any somatic cell type where ES cells did not exist. It was the success of SCNT that also led to the derivation of induced pluripotent stem cells (iPS), also from many somatic cell types. Spermatogonial stem cells, which can be grown in culture, genetically altered and then single cells expanded into lines that can be characterised before being re-introduced into testes to make sperm, then became a route to altering the genome, as demonstrated in, for example, mice and macaques. Substantial progress has also been made in deriving gametes (eggs and sperm) entirely *in vitro* beginning with ES cells or iPS cells.

Dr Lovell-Badge raised his opinion that researchers had never set out to develop methods that would specifically genetically alter humans, and instead identified some of the developments and drivers he believed had driven this technology. These have included:

- Basic curiosity about how genes are expressed during development and in adults
- Stem cell biology
- The role of specific genes in embryo development, in physiology, in the immune system and the brain etc.
- The aetiology of genetic diseases
- Practical applications in farm animals.

Genome editing methods make use of endogenous DNA repair mechanisms and require:

- The use of "molecular scissors"- a nuclease enzyme to make a double-stranded cut in the DNA.
- A "homing device" – a mechanism to recognise specific DNA sequences, derived from DNA binding proteins such as transcription factors or complementary RNA.
- A "template"- if more than a simple "indel" mutation is required, a DNA template with homologous arms is needed to allow homology directed repair.

Genome editing systems have progressed from the use of meganucleases, to ZFNs (Zinc finger nucleases) to TALENs (Transcription Activator-Like Effector Nucleases) to the current use of CRISP-Cas9 (Clustered regularly interspaced short palindromic repeats.) With CRISPR-Cas9 it has proved much simpler to make the necessary components – guide RNAs, Cas9 and DNA templates. The technique is very versatile. It is also relatively simple to introduce these into cells and early embryos. It is highly specific, but off-target events may still be an issue. Data suggests that these events may be very rare, and they are not found in cell lines derived from single cells, or in mice made after zygote injection, but for somatic gene therapy where many millions of cells need to be edited, they could be a problem. Whilst CRISPR-Cas9 is also highly efficient, there is still the possibility for mosaicism to occur when the components are introduced into early embryos.

Dr Lovell-Badge suggested a number of potential reasons for the genome editing of human cells (including those of the germ line, and early embryos). These include:

- Basic understanding of human biology and of the role of specific genes and processes.
- To create and study models of human genetic disease *in vitro.*
- To treat disease (somatic cells).
- Germline changes to avoid/prevent genetic disease.
- Germline alterations to give "genetic enhancements".

Numerous experiments can be carried out *in vitro* to provide an understanding of human biology. These can be used to:

- Study the role and mechanism of action of specific genes or gene pathways.
- Understand specific processes, such as cell-cell interactions, cell movement, cell lineages and how these are specified.
- Make use of stem cells *in vitro* to screen for molecules that can either influence these processes in a beneficial way, or which are harmful.

There have been many publications describing the creation of new disease models using CRISPR-Cas9. Much work is already taking place *in vitro* with a variety of human cell culture systems to better understand human biology, including, for example the use of:

- Organ-specific stem cells e.g. neural and gut stem cells.
- Embryonic stem cells (ES) and induced pluripotent (iPS) stems cells, which can be differentiated *in vitro* to
- Complex tissues (cortical brain structures, optic cups, kidney-like structures etc)
- Specific cell types (neurons, primordial germ cells etc)

As a result of these studies, the same techniques could be used to study pre-implantation embryos and other germline cells. For example, recent studies have carried out comparisons of blastocyst and early post implantation development between mouse and human, and have examined the growth factor conditions and stem cell development in early mouse and human embryos.

Bringing his wide-ranging review of the science of genome editing to a conclusion, Dr Lovell-Badge summarised some of the ongoing areas of research and their potential future applications. Key studies are investigating:

- How cell types are specified in the early human embryo, and the nature and importance of the genes involved. This work could lead to improved techniques for culturing embryos following IVF, better implantation rates and fewer miscarriages.
- The biology and genetics of stem-cell lines representing the cell lineages thought to exist in the early human embryo. This could lead to an improved ability to establish stem-cell lines for research, the screening of drugs for embryo/placenta toxicity or beneficial effects to prevent miscarriage. It would also help to reduce the number of embryos needed for research.

Reflecting on a common ethical concern, Dr Lovell-Badge also reasoned that as research in genome editing techniques is leading to improved efficiency and versatility of genome editing in embryos and germline cells, this could in turn lead to a reduction of embryos required for such studies.

Specific comments arising from the presentation from Dr Lovell-Badge

Noting that the *in vitro* studies on genome editing in the human embryo were being carried out in China and have been authorised in the UK and Sweden at present, general concern was raised again that EU-wide funding for such important studies was not forthcoming under H2020. The possible role of non-human primates (NHPs), instead of human cells in research studies, was raised. Dr Lovell-Badge suggested that the benefits of using NHPs was limited, mainly because researchers currently knew far more about the human than the NHP in this field, and because there may be differences in the biology of early human and NHP embryos, such as in specific trophoblast cell types. The ethical issue of using primates when human cells were available also had to be considered. The importance of obtaining better availability of safety data from *in vitro* studies before entering the clinic was emphasised, particularly in connection with the possibility of off-target effects.

In his presentation Dr Lovell Badge had indicated that it was relatively easy to introduce the necessary components – guide RNAs, Cas9 and DNA templates into cells and early embryos using CRISPR-Cas9. There was much discussion at this point (and throughout the workshop) about how delivery mechanisms do however still need to be improved and therefore efforts to further improve such delivery mechanisms should not be neglected.

Session 2: Panel Discussion: Exploring different perspectives on the use of genome editing for basic research in the EU

Chair: Professor Virginijus Šikšnys (Vilnius University)

Introductory comments from panel members

Ruth Mampuys (Coordinator, Ethics and Societal Aspects, at the Netherlands Commission on Genetic Modification, COGEM)

The Netherlands Commission on Genetic Modification is an independent scientific advisory body which provides advice to the government on the risks to human health and the environment of the production and use of GMOs. It also informs the Government on the ethical and societal issues linked to genetic modification. COGEM and the Dutch Health Council organised a symposium on human genome editing in November 2015 and a report on the potential for human genome editing in the Netherlands and the implications for its governance is expected to be published early in 2017.

In the Netherlands, both the EU GMO legislations and the national Embryo Act are relevant to the regulatory landscape for human genome editing. The GMO regulations are, in general, similar to those of other Member States. Research with embryos and gametes is covered under the Embryo Act and must undergo a review every few years by the Central Committee on Research Involving Human Subjects (CCMO). The GMO legislation defines a GMO as an organism, with the exception of human beings, in which the genetic material has been altered in a way that does not occur naturally by means of reproduction or natural recombination. Humans are exempt from the GMO legislation. Under Dutch law it is prohibited to alter the nuclear DNA of germline cells that are to be used for a pregnancy. This is in line with the Oviedo convention, which was signed by The Netherlands (but not ratified).

(Post meeting note) The Minister for Health had previously announced that the Dutch government had decided not to ratify the Oviedo Convention, amongst others, because of its categorical prohibition on the creation of embryos for research and the prohibition of genetic material alterations and transfer, because this would hamper research and clinical use of techniques to avoid amongst others mitochondrial disorders.[3])

Research with surplus embryos is allowed under strict conditions. Gametes and embryos that are no longer going to be used in a pregnancy e.g., following IVF treatment, can be used for research and for culturing embryonic stem cells. The consent of those from whom the embryo was originally intended is required. Research on such human cells is subject to a number of conditions including that there must be no alternative research method available and that prior approval from the Government and the CCMO is needed.

The Embryo Act prohibits the cloning of human beings and the creation of human-animal chimeras. Under the Act it is prohibited to allow embryos to develop outside the body for longer than 14 days. The Act also prohibits the generation of embryos especially for scientific research, and prohibits the alteration of genetic material in the nucleus of gametes of embryos that are intended to be used for a pregnancy. The specification of the nucleus was intentional to leave room for the potential application of techniques to prevent mitochondrial disorders.

There have been very few applications for the use of human embryos in basic research (approximately 1-3 reviews p.a. to date) So far there have been no applications to the CCMO regarding genetic modification of human embryos.

The ban on creating embryos for research purposes was debated when the Embryo Act was reviewed in 2012, but it was felt at the time that it was too early for any decisions/changes on this matter. A 2015 report concluded that in certain circumstances the creation of embryos is necessary for scientific progress. (*Post-meeting note:* The Dutch Minister of Health, in a letter of 27 May, proposed to change the embryo act to allow the creation of embryos for very specific research purposes with direct clinical relevance (the prohibition remains for fundamental research). A draft amendment of the law is expected in November.)[4]

Ms Mampuys also noted that public opinion regarding the ethics of embryo research and genome editing may be changing. She highlighted that a public opinion survey, performed in 2008, on the use of embryos for research found that almost 50% of the population was against the creation of embryos for research. However, a more recent (albeit much smaller)

[3] https://www.rijksoverheid.nl/documenten/kamerstukken/2015/03/20/kamerbrief-over-standpunt-ratificatie-biogeneeskundeverdrag.html

[4] https://www.rijksoverheid.nl/binaries/rijksoverheid/documenten/kamerstukken/2016/05/27/kamerbrief-met-kabinetsreactie-op-rapport-over-wetenschappelijk-onderzoek-embryo-s/kamerbrief-met-kabinetsreactie-op-rapport-over-wetenschappelijk-onderzoek-embryo-s.pdf.

public poll suggested that 65% of the Dutch public would allow repairs to genes before birth, at the embryo stage.[5]

Professor Ernst-Ludwig Winnaker (German National Academy of Sciences 'Leopoldina' and the Ludwigs-Maximilians-Universität München, Germany)

Professor Winnaker provided a brief overview of some of the current activities of the Leopoldina in contributing to the ongoing debate in Germany on the science and regulation of genome editing. As had been previously noted in the workshop, the situation regarding the regulation of such a technology and of the use of embryos was somewhat difficult. The restrictions of the Embryo Protection Act meant that embryos cannot be used for anything other than pregnancy. There are however far fewer limitations on the use of somatic cells, and so the Leopoldina and the German research funding agencies have been working on a joint position paper to encourage more research on their use in basic research.

The Leopoldina recently added its voice to those who were calling for a moratorium on germline genome editing.

Research on embryos in Germany is very limited, and it was further noted that this restriction extends beyond national borders as German citizens are not allowed to work overseas on embryo research if that work was funded by Germany's funding agencies. As had been suggested earlier in the meeting, German postdoctoral researchers carrying out such work on embryos in laboratories overseas could face many difficulties in continuing a research career in Germany on their return, but there was a lack of clarity over the real ramifications of the current legislation.

Professor Winnaker acknowledged that there were many inconsistencies in the relevant legislation in Germany, but reasoned that this was to be expected as the regulations had been in place for more than 25 years, and therefore outdate recent technological advances. As such research was regulated in Germany through the use of formal regulations, the support of Government would be required for any changes. It was quite difficult to influence politicians on the need to carry out such research and why the legislation should be amended to reflect the changing nature of science.

It was considered unfortunate that the legislation in place in individual Member States influenced the funding of research by the European Commission, through its European Research Council and other funding instruments, and it was suggested that it was timely for this to be reviewed

Dr Robin Lovell-Badge (The Francis Crick Institute, London)

In the UK the Human Fertilisation and Embryology Act 1990 regulates research on human embryos and gametes. The law works by a general prohibition and qualified permission. No human embryo research may be carried out without a licence from the HFEA. The 2008 version of the Act clarified many of the conditions for such research and it is now possible under the Act to use genome-editing techniques in embryos. Any embryos donated for research purposes are subject to the informed consent of the donor. Research on gametes has historically been outside the scope of the Act and, since 2009, exemptions have existed for keeping gametes for the purposes of research where fertilisation is not involved.

A number of the UK's major research funders and professional bodies, including Wellcome, Medical Research Council and the Academy of Medical Sciences recently published a public statement to demonstrate their support for the potential beneficial application of human

[5] http://dekennisvannu.nl/site/artikel/Uitslag-publieksonderzoek-zo-denken-wij-over-genmodificatie/8132

genome editing and the importance of continued support for basic research in this field using human embryos. The current restrictions on such research in many Member States, and the unwillingness of the European Commission to fund research in this area were considered unfortunate.

Professor Giuseppe Testa (European Institute of Oncology, and European School of Molecular Medicine, Italy)

He described some of the current complexities of the Italian regulatory process for such research. In Italy, Law 40 of the 2004 legislation on assisted procreation had previously regulated much of the research carried out on *in vitro* fertilisation. The Constitutional Court of Italy had over the years gradually removed many of the constraints upon research that were within the Act, including its decision in June 2015 to lift the ban on the accessing of pre-implantation genetic diagnosis. However, the prohibition on the use of human embryos in research still stands.

The modification of gametes was prohibited unless it was for the "improvement" of the gamete. Reference was made to the recent prohibition of a woman in Italy who had wanted to donate embryos, obtained from her IVF programme, to research. This matter had been forwarded to the Italian Parliament to agree a way forward, but no progress had been made, and a major disconnect remained between the Government and the pace of research. Whilst it was clearly recognised that there was a need for more dialogue with the public on governance of genome editing research, and the use of embryos in research in general, it was felt that this would be difficult to progress in Italy at present.

Session 2: General Discussion

It was noted that there had been no apparent distinction made, in Germany, between the governance of disease treatment, versus "enhancement" of individuals using somatic cell therapy. Such "enhancement" could include the improvement of athletes' performance through the promotion of muscle growth or the increase in EPO production. This was the first instance, of several throughout the workshop, where the importance of language was noted. Many recognised that the development of consistent definitions and a shared lexicon could be beneficial to the field - both nationally and internationally. In light of the current restrictions on embryo use in Italy, it was unclear whether research carried out in other countries, such as the UK, in genome editing, would be published in an Italian journal? It was understood that the recent studies on CRISPR-Cas9 by the scientists in China had not been published in any national scientific paper in Italy. Concern was raised over suggestions that telephone conversations on possible future collaborative research proposals between scientists in a EU Member State where embryo research was prohibited, and those countries where such research was allowed, in itself could lead to prosecution.

Session 3: Clinical research and applications in human somatic cells – current state, opportunities and regulation

This session was designed to explore the current state of genome editing, the potential opportunities afforded by such techniques, and any regulation governing their use within the context of clinical research and clinical use involving human somatic cells.

Chair: Professor Luigi Naldini (Director, Division of Regenerative Medicine, Stem Cells and Gene Therapy, San Raffaele Scientific Institute, Italy)

Introductory comments from Professor Naldini

Professor Naldini provided an overview of the development of the techniques used in this field, including *ex-vivo* and *in vivo* genome editing, *in situ* correction of disease causing mutations, targeted transgene insertion and gene disruption.

- In *ex vivo* genome editing, cells are isolated from the patient, treated *in vitro,* and then infused/transplanted back into the individual. The cell source is autologous or allogenic. The cell types used are either:

Somatic stem cells, allowing tissue repopulation with their genetically modified progeny (including haemopoietic, neural, epidermal or corneal, or mesenchymal stem cells), or Differentiated cells. In these cells, immune effectors can be genetically modified to enhance activity against tumours or infectious agents.

- In *in vivo* genome editing there is a need to administer the genome editing machinery into body fluids, cavity or organs in order to modify some tissues *in situ*. The target cells are long-lived tissue cells such as muscle fibres, liver hepatocytes or neurons of the central nervous system.

Professor Naldini went on to more specifically detail some examples where genome editing may have clinical value. For example, he explained that genome editing, to correct a mutated gene *in situ*, may eventually outperform current gene therapy techniques which more simply aim to replace (but not correct) mutations. He explained that, in terms of safety, gene editing may abrogate the risk of insertional mutagenesis of gene replacement vectors. He added that genome editing is also widely applicable to stem cell-based therapies, but cautioned that it currently falls short of reaching the same efficiency, given the lower efficiency of HDR-mediated editing *vs.* gene addition.

In another approach, targeted transgene insertion, there is a targeted integration of transgene expression cassette into a safe genomic harbour. This is conducive to robust transgene expression; it allows safe insertion that does not affect flanking genes, nor does it have any detrimental influence. It ensures a predictable robust expression of the therapeutic gene. The technology is potentially widely available to *ex vivo* cell-based therapies (stem cells in particular) and to at least some tissues *in vivo*

Professor Naldini also explained that as current gene therapy techniques involve the addition of genetic material, they are rarely suitable in scenarios where a disruption of a gene may be the desired outcome (i.e. in the case of treating a dominant disease). He therefore noted that gene disruption offers a unique application of gene editing versus standard gene therapy strategies, and can be currently achieved with significantly higher efficiency than HDR. Some clinical trials are already ongoing, with some indication of benefits for edited T-cells, and these may soon be extended to HSC. One of the clinical studies is seeking to disrupt cytokine receptor/co-receptors for HIV infection, making the T-cells of an HIV-infected individual resistant to viral infection. Other studies are looking at the possibility of

disrupting an endogenous repressor (BCL11) that may release expression of a gene compensating for a mutant one - in the possible treatment of thalassaemia and sickle-cell anaemia.

In T-cell immunotherapy there is great promise of gene editing. Initial evidence of its potential benefit has already been shown in the treatment of a child in the UK affected with leukaemia.

In vivo gene disruption has not been tested as yet in the clinic. It could be used for example for the reconstitution of a functional dystrophin in DMD by forcing skipping of the exon carrying the disease-causing nonsense mutation (through NHEJ-mediated disruption of the upstream slice signal or deletion encompassing such an exon.)

Session 3: Panel discussion: The different perspectives on genome editing in human somatic cells in the eu

Introductory statements by panel members

Professor Nathalie Cartier-Lacave (INSERM and the European Society of Gene and Cell Therapy)

ESGCT, in collaboration with the Japanese and Finnish Societies for Gene and Cell Therapy, and the Alliance for Regenerative Medicine had discussed the scientific, ethical and social issues relating to germline gene editing at its Annual Congress in Helsinki in September, 2015. That discussion had reflected on a number of issues as to where the technology could and should be used, as well as identifying those areas of research where it was felt it should not be applied at present. There had been general agreement at that time that there should be a clear divide between the use of genome editing in basic research and its potential use in the clinic. As research in genome editing moves from research towards clinical use it was felt essential to engage the public more in understanding the potential benefits and implications of its application. ESGCT acknowledged that the science of genome editing was very fast moving and that the current technologies being used may soon become superseded. There were some doubts as to whether the current regulatory framework for all aspects of genome editing was really fit for purpose.

The American and Japanese Societies of Gene Therapy issued a joint position statement on human genome editing in 2015. Those societies had concluded that it wasn't ethically acceptable to conduct gene editing in the embryo or to make any other germ-line modifications because the results of such studies could not be evaluated effectively in an acceptable timeframe. The societies had called for a ban on human germ-line gene editing until all relevant technical and ethical problems had been addressed and consensus by all parts of society had been reached.

Professor Cartier-Lacave reported that ESGTC did not support such a moratorium at this time, but firmly welcomed further discussion on all aspects of the development of the technology.

Professor José Garcia Sagredo (University of Alcala, and Member of the Spanish Royal Academy of Medicine.)

Professor Garcia Sagredo presented an overview of the regulatory systems currently in place in Spain governing the use of genome editing in research and in clinical use involving human somatic cells. He noted that "genome editing" *per se* is not referenced in the legislation (as it is a new technique) and hence there are no specific guidelines as to its application. The Spanish Penal Code (10/1995), last reviewed over 10 years ago, prohibits genetic manipulation (with possible imprisonment for transgressors) unless it is for gene therapy, and for purposes other than the elimination or reduction of defects or serious illness. Another key article of the Penal Code (Art 160) prohibits the cloning of human beings.

Spain signed the 1997 Oviedo Convention on Human Rights and Biomedicine and thus continues to comply with its restrictions.

It is possible to carry out research in Spain using stem cells, gametes and embryos, within the limits of the Assisted Human Reproduction Techniques Act (14/2006) and the Biomedical Research Act (14/2007). Under these laws the creation of human embryos for research is not allowed, but the use of donated embryos less than 14 days old, is allowed. These experimental embryos cannot be implanted. All such research must be approved by local research ethics committees or the National Commission for Assisted Reproduction of the National Ethics Research Committee.

Post-meeting note: It has been suggested that in Spain, although embryos produced by somatic cell nuclear transfer (i.e. via the cloning procedure) cannot be transferred to obtain a child, as they do not fit the Spanish definition of an embryo, they are available for research.

Article 13 of the Assisted Human Reproduction Techniques Act (14/2006) permits therapy performed in pre-embryos only if it does not alter the 'non-pathological hereditary characteristics', nor 'look for the selection of individuals or the race'.

Regarding somatic cells, the rules on obtaining, conservation and implementation of tissues is regulated by the Royal Decree (9/2014). Cell therapy is regulated by another Royal Decree (223/2004), which regulates clinical trials with medicines.

For clinical trials, Article 47 of the Advanced Therapy Medicines legislation clearly distinguishes between somatic cell therapy and gene therapy. The European Directive on clinical trials (536/2014) has been transposed into national legislation by the Royal Decree 190/2015.

In Spain, the Medicines Use Law (10/2013) and the Biomedical Research Act (14/2007) provide the regulatory framework for gene therapy in humans. The Royal Decree Law (9/2014) regulates the standards of quality and safety for the donation and use of human tissues. These regulations would cover cellular therapy and gene therapy, but do not address genome editing *per se.* Article 17 (Requirements for clinical trials) of the Royal Decree (1090/2015) states that clinical trials with gene therapy that produces modifications in the genetic identity of the germ line of the person are prohibited. Professor Garcia Sagredo explained that the main driving forces in Spain for decisions on regulations in this whole field include various scientific societies, hospitals and research

centre research and ethics committees, in addition to the key role played by public opinion. He added that, at present, there is no work being taken forward by the scientific Academies to review or change the legislation.

Professor Garcia Sagredo explained that public opinion (where it can be measured) seems to be supportive of gene therapy and PGD, with such advances in healthcare strongly promoted by patient associations. Ecology groups, who do have an impact on the Spanish media, and therefore public opinion, are more concerned over the development of genetically modified (GMOs) animals and plants. As noted by other delegates throughout the meeting, Professor Garcia Sagredo suggested that the use of language plays an important part in influencing public opinion, with emotive terms such as gene or embryo 'manipulation' likely to be seen as pejorative, whereas therapeutic approaches to rare diseases will be seen as beneficial.

In summary, genome editing is being used in human somatic cells within both research and clinical capacities in Spain, and has been used both to produce models to better understand the pathophysiology of various diseases (including tumours, spastic paraplegia), and in pre-clinical gene therapy studies in disorders such as Epidermolysis bullosa, Fanconi anaemia and DMD.

Dr Verónica Martínez-Ocaña (Scientific Officer, Ethics Sector, European Research Council)

Dr Martínez-Ocaña described the role of the European Research Council (ERC), one of the funding mechanisms of the EC's Horizon 2020 (H2020) programme. She explained that the ERC's mission is to encourage the highest quality research in Europe through competitive funding and to support investigator-driven frontier research across all fields, on the basis of scientific excellence. The ERC complements other funding activities in Europe such as those of the individual national research funding agencies, and is a flagship component of H2020.

The ERC's funding schemes are 'investigator-driven' taking a 'bottom-up' approach. There are no thematic priorities, nor is the direction of the research set by politicians. Researchers are able to identify new opportunities and directions in any field of study. To organise the evaluation of the proposals, the ERC has established 25 scientific panels, grouped into three main domains: Physical Sciences and Engineering, Social Sciences and Humanities, and Life Sciences.

Dr Martínez-Ocaña noted that the ERC is funding increasing numbers of projects using the new genome editing technologies, especially the CRISPR-Cas9 technique. In a preliminary analysis carried out on the three main funding schemes of ERC (Starting, Consolidator and Advanced Grants) during 2015 calls, it was shown that across these granting schemes, 40% of the funded proposals in life sciences are using CRISPR-Cas9. The breakdown was as follows:

- Starting grants – for a total of 330 grants, 114 were on life sciences and of these 33 included the use of CRISPR-Cas9 technology (33%)
- Consolidator grants – from 302 grant applications, 94 were on life sciences, and of these 44 included the technology (47%).
- Advanced grants – for a total of 277 grants, 92 were on life sciences, 44 of which included CRISPR-Cas9 (48%).

Dr Martínez-Ocaña went on to explain that all projects need to undergo ethical review before funding can be awarded. Analysis of the ERC grant applications shows that the CRISPR-Cas9 technology is being applied on many different fields within life sciences. A very high percentage had some application for human health. The technology is being applied on basic research to elucidate molecular, cellular, physiological and pathophysiological processes. The technology is also being used in pre-clinical research in which CRISPR-Cas9 is used to

create disease models to better understand the pathophysiology of a disease, to develop better diagnostic techniques and to assess new therapeutic strategies.

Session 3: Clinical research and applications in human somatic cells – current state, opportunities and regulation

It was suggested that there was a need for more research investment in the development of novel delivery mechanisms.

It was noted that despite there being a large body of legislation in Europe for the regulation of somatic cell gene therapy, the first use of such a technology (in the UK) went around the regulations, and made use of a 'compassionate use' approach. This would have been somewhat disappointing for the Regulatory Agencies seeking to govern this new technology effectively.

It was suggested that there was some pressure, globally, to get these treatments into the clinic quickly. If things were to go wrong in such clinical use it would have a major and long-term negative impact on the uptake of the technology.

There was much discussion on whether the EU was a good environment for the development of somatic cell gene therapy. It was suggested that the absence of a clear regulatory framework for such a therapeutic approach could limit the number of new treatments in this field going forward within the EU. Some doubts were raised over the relevance of the current gene therapy regulatory framework for the regulation of genome editing-based therapies as the former was more focused on assessing the safety of viral vectors. It was not believed either the scientific community or the public were pushing for 'easier' legislation. In considering the applicability of the Advanced Therapy Medicinal Products Regulation to this field, it was noted that most applications have been dealt with via exemptions. The EMA were keen to ensure that the current approach to regulation was continually improved. The Commission was not likely to open the legislation for further changes.

There was some discussion on the EU Clinical Trials Regulation going forward. In future, evaluation would be done at the European level, and individual member states would not be able to refuse to allow the carrying out of any clinical trial. But, if most EU member states were opposed to gene editing studies, it could make it hard to do such trials in Europe, when the new Regulations come into force.

In response to a question raised about the ownership of the CRISPR-Cas9 intellectual property, and whether this would be an issue for European scientists wishing to use the technology, it was suggested that the ongoing patent debate was not considered likely to have an effect upon any early-stage research programmes going forward.

Session 4: Clinical research and applications in germline cells – current state, opportunities and regulation

Professor Pierre Jouannet: Clinical research and applications in germline cells – current state, opportunities, challenges and regulation

This session was designed to explore the current state of genome editing, the potential opportunities and challenges afforded by such techniques, and any regulation governing their use within the context of clinical research and clinical use involving human germline cells.

Chair: Dr Robin Lovell-Badge, Francis Crick Institute

Professor Jouannet observed that most discussions on the governance of germline cell modification research tend to focus on the embryo. This is understandable if the cells were to be edited for reproductive purposes, but if the embryo was not to be transferred into a uterus, the concern should be different.

Both recently published Chinese studies had used abnormal (tripronuclear zygotes) embryos that were be unable to lead to the production of a child. Their aim was only to better understand the CRISPR-Cas9 uses and limits. The first study by Liang *et al* has shown low efficiency of homologous recombination directed repair (HDR), evidence of mosaicism in the edited embryos, and off-target effects. In the second study by Kang *et al*, NHEJ-mediated indel mutations were obtained with a high efficiency, but lower efficiency of HDR-mediated modifications. The other alleles at the same locus either were wild type or contained indel mutations. No off-site targeting was detected for a total of 28 potential off-target sites.

The potential clinical applications of human genome editing techniques that can affect the germline include:

- Preventing the transmission of a particularly serious hereditary disease to a child when PGD is unavailable because one parent is homozygotic for a dominant autosomal disease, e.g. Huntington's chorea, or both parents are homozygotic for a recessive autosomal disease, e.g. with cystic fibrosis, but this would be very rare.
- Editing of abnormal embryos when PGD revealed no embryos without the mutation
- Reducing the risk, or protecting individuals, from the development of common diseases
- Promoting specific characteristics or traits in the future child.

No editing technique described until now has the efficiency and the safety required to use them on human embryos with the goal of creating a child. In the creation of small mutations (indels) in animal models, frequencies of up to 100% have been described. However, until recently, in most species in which experimental embryo genome editing had taken place, (and particularly for homology directed repairs where a DNA template was also required) the desired genomic modification has been found only in a minority of newborn animals. This is becoming more efficient and frequencies closer to 50% or even higher are being obtained. Nevertheless this would still not be acceptable in its application in humans, where it would be essential to have 100% efficiency at birth and no off-target effects.

Many ethical issues were related to human germ line genome editing. These depending upon whether the study was for basic or pre-clinical research purposes or whether there was a clear clinical application in mind. They also depended upon the embryos or cells being edited. Some countries banned any kind of research on human embryos but authorized research on germ cells before fertilisation. Others have made possible research only on those embryos that were developed within the framework of Assisted Reproductive Technologies (ARTs). In a few countries, such as UK and Belgium (and perhaps soon the Netherlands), research may now be done on human embryos that were created solely for research purposes.

Ethical considerations could vary also on language and definitions. For example, it was noted that in Germany it was legally acceptable to freeze zygotes, but not embryos.

Looking at the clinical applications relating to genome editing performed on human germ cells and embryos, the current ethical questions need to be examined at the light of other modifications which could be done on a human embryo before its transfer into the uterus, e.g. through chemical treatment or through invasive intracellular procedures. Should any modification of the embryo that has consequences that are potentially transgenerational be excluded as a matter of principle?

Isn't a European consensus an unattainable challenge when looking at the possible discrepancies between the provisions of the Oviedo Convention (1997) and its application? Article 13 (Interventions on the human genome) of Chapter IV, the Council of Europe's Convention on Human Rights and Biomedicine, states that "An intervention seeking to modify the human genome may only be undertaken for preventative, diagnostic or therapeutic purposes, and only if its aim is not to introduce any modification in the genome of any descendants". At the same time, Article 18 (Research on embryos *in vitro*) in Chapter V (Scientific Research) states that "where the law allows research on embryos *in vitro*, it shall ensure adequate protection of the embryo". Could the correction of a gene mutation that would otherwise have disastrous consequences be considered as an adequate protection of the embryo?

It was noted that for different reasons, both the UK and Germany had neither signed nor ratified the Oviedo Convention. Other countries had signed it, but had yet to ratify it.

Session 4: Panel discussion on the different perspectives on genome editing in germline cells in the eu

Initial statements by panel members

Professor Bernard Baertschi (University of Geneva)

Reference was made to the use of Citizen Votes in Switzerland on such key ethical issues. The Swiss Constitution makes genome editing of germline cells unlawful. It is illegal to create embryos and to use 'surplus' embryos derived from ART for research. Whilst research using human embryos is illegal, that using human embryonic stem cells is allowed – but there are very few such stem cells available to researchers. Research on HESC is considered controversial and it is difficult to get public research funding for such studies. There were only 11 of such projects ongoing at this time, and whether any of these was using CRISPR-Cas9 was unknown (to the speaker).

Professor Baertschi noted that, in Switzerland, public debates on this topic were linked into people's concerns over eugenics and new GMO-related plant breeding techniques, as well as more positive approaches to the development of pre-implantation genetic diagnosis (PGD) which used to be banned in Switzerland until the public vote in 2015. The Swiss Academy of Sciences had played an important role on the matter and has for the most part relayed the position of the German Academies.

He added that the Swiss public appeared divided in their views on the development of such techniques as CRISPR. Whilst the potential benefits for health are often recognised, there are concerns over its possible impact on the environment, as in the control of mosquitoes. Usually, the Swiss people approve biotechnologies when they are used in the service of human health, but not in other domains. Some references to the possible uses of CRISPR-Cas9 in the furtherance of 'eugenics' had been made in the media.

Others had expressed concerns over the safety of using such genome editing techniques in humans, with some groups worried about scientists 'playing God'. It was also felt by some that at present the application of genome editing was less efficacious than the use of PGD in order to manage serious foetal conditions.

Dr Peter Mills (Nuffield Council on Bioethics, UK)

Dr Mills emphasised that his comments were focussed on the very specific ethical and regulatory framework that currently existed in the UK – a framework that may not be relevant or applicable to other countries.

He explained that there is a strong public interest in the UK in the ethical aspects of genome editing in germline cells. This public interest - and the interests of different publics - are exhibited in a number of engagement initiatives that have taken place in the UK (e.g. around PGD, mitochondrial donation, etc.). UK public opinion appears to be cautiously progressive, that is, that it has a more 'normal' distribution and is not polarised in the way that it is in the US, but that this distribution is conditional on confidence in the fact that the practices in question are effectively and responsibly regulated. It is also harder to directly correlate these views from the UK (which may have a different moral tradition to most of Europe) with those from other EU countries, particularly those that have ratified the Oviedo Convention.

The UK framework for the regulation of genome editing in human embryos works through a process of prohibition and licensing by the HFEA. All such research is prohibited, unless a licence is given. In the UK genome editing would be regulated as a research tool like any other, but in all such cases the use of embryos still has to be shown as necessary or desirable for one of the statutory purposes set out in the framework legislation (the Human Fertilisation and Embryology Act 1990). To date the Authority has only licensed one research project in this field.

Reflecting on how best to address the ethical concerns raised by genome editing, Dr Mills noted that the UK has had the 'benefit' of a recent and lengthy review of the regulatory framework as it applied to embryological techniques for the avoidance of mitochondrial disease, from which it is possible to draw parallels. This review involved much debate among the public and in Parliament, with considerable intervention from experts from a wide range of opinion and specialism.

The recently approved regulations now permit mitochondrial replacement techniques to be used clinically in order to avoid the inheritance of mitochondrial disease; however, the clinical use of genome editing techniques to alter nuclear DNA would require a change in primary legislation. There is no sign of this happening at present.

Professor Pierre Jouannet (French Academy of Medicine)

Based on the legislation introduced in France in 1994, it should be impossible to edit human germ cells or embryos for clinical application and it was not possible to create embryos for research. A number of scientific organisations in France are however currently looking into this matter, and are seeking to make research legally permissible to carry out genome editing on germline cells. Patient groups had not been that involved in the debate on genome editing in France until now.

Dr Anna Veiga (Centre for Regenerative Medicine, Barcelona)

Dr Veiga briefly summarised the legislation and governance structures that are in place in Spain. In addition to it being a signatory to the Oviedo Convention, since 2004 Spain is also subject to legislation on the use of embryos in research. The Assisted Human Reproduction Techniques (ART) Act (14/2006) and the Biomedical Research Act (14/2007) also impacted upon the use of genome editing techniques in the clinic. It was noted that the governance issues regarding research applications frequently got mixed up with those concerning clinical applications. It was felt that the legislation had become somewhat out of date for it was established before genome editing techniques had been developed.

With respect to the possibility to perform genome editing for therapeutic purposes, a contradiction between ART legislation and the Oviedo convention is noted in Chapter III of Article 13 of the 14/2006 Law on Assisted Reproduction. This chapter refers to therapeutic techniques in the pre-embryo and they are allowed provided that their aim is for treating a disease and preventing transmission. The requirements include an Informed consent, that they are indicated for the treatment of well diagnosed diseases with a severe or very severe prognosis and adequate chances of success and that there is no modification of non-pathologic traits (to avoid eugenics). They have to be performed in authorised centres, by skilled professionals with the previous authorisation by competent authority and National Commission for ART.

All research applications needed to be approved by local Research Ethics Committees or by the National Commission for Assisted Reproduction. At this time no proposals for research or clinical application had been submitted for approval.

Professor Ewa Bartnik (University of Warsaw, Poland)

Professor Bartnik summed up the current regulatory system in Poland as 'nothing is allowed', particularly in connection with the use of embryos in research or clinical application.
In Poland the embryo is classed as a 'conceived child' and is protected from the start.

Poland has signed the Oviedo Convention, but has not ratified it as yet. This is being looked into by an expert committee. It is illegal for clinicians to participate in experiments on embryos, but new legislation is being implemented on infertility treatment.

It is forbidden to derive human embryonic stem cells in Poland, but there is no legislation preventing them being imported to the country from elsewhere.

Session 4: General Discussion

The panel was asked about what legislation was in place within the EU that governed research on a foetus whilst it was in the uterus. It was not thought that there was any such legislation, although the EMA would consider such a study as a clinical trial on a pregnant woman. The lessons that had been learnt from the public engagement programme carried out by the UK's Human Fertilisation and Embryology Authority were discussed. It was noted that HEFA had carried out various public consultations, market research studies and detailed surveys and that this way typical of the way regulatory policy was developed in the UK.

Concerns over genome editing "treatment tourism" were raised, as it was acknowledged that this was already widespread for PGD – with patients going elsewhere for treatment.
In assisted reproduction there was usually a need for payment. The relevance of EC Directives on cross-border health and the cross-border movement of patients were noted.

The importance of effective engagement with patients and patient groups was discussed. There was general agreement that it was essential for more to be done to explain the new scientific terminology in the field to patients to help them better understand their conditions

and if and how genome editing could help or not in the future. Groups such as Eurordis and EGAN were doing much in the field. This was felt to be important in light of the possible establishment of 'rogue clinics' who may start to offer false treatment.

The possibility of identifying a model governance framework for genome editing was considered. It was suggested that the UK model of legislation had worked well, but the fact that the Oviedo Convention was now binding legislation in many of the EU Member States was an important factor. Article 28 of the Convention was considered to be a good starting point for going forward. The Oviedo Convention has arisen out of the human rights tradition (and is dependent on the ECHR), but in the context of human genome editing it would be important to ask what was 'contrary to human dignity'.

Concern was raised over the large number of human embryos that were destroyed each year in Europe (>150,000 p.a in a single country such as France) and why this was ethically more acceptable than to allow such IVF donated embryos be used in healthcare research?
Whilst it was acceptable for such embryos to be used this way in some Member States, the European Commission was not in a position to support such research across the EU in light of the wide variation in the regulatory and ethical landscape across the EU. It was noted that there were no EU-wide limitations on the movement of embryos from one Member State to another for research purposes, but that researchers needed to abide by the laws of each country involved.

Session 5: Human genome editing cross-sector issues

Following comprehensive discussions throughout the day, this final session provided an additional opportunity to foster cross-sector discussion regarding human genome editing. Panel members were drawn from a range of relevant stakeholders beyond academia, and included regulators, industry, funders, and patient groups.

Chair: Professor Ernst-Ludwig Winnaker (Ludwigs-Maximilians-Universität München, Germany)

Introductory comments from panel members

The Regulatory Perspective: Dr Nicolas Ferry (EMA)

Dr Ferry noted that there are two key bodies in the EU likely to be involved in the regulation of potential clinical studies of genome editing applications; one concerned with the regulation of any medicinal product *per se* and that which oversees the implementation of the Clinical Trial Regulation, which comes into force within the next two years. Once a research application becomes a product, the relevant EU-wide regulations have to be followed: there is no national subsidiarity. The Advanced Therapy Medicinal Products (ATMPS) Regulations cover somatic cell and gene therapy derived products. The EU Tissues and Cells regulation regulates only the collection, storage and distribution etc., of cells, but not any clinical trial use.

Whether gene editing should fall under the same regulatory class as gene therapy was still under discussion within the EU. There would still be a requirement to provide data on safety for example, especially if *in vivo* editing was being carried out. In most cases the cells being used would be classed as genetically modified organisms (GMOs).

It was noted that there was little regulation in place as yet concerning genome editing of germ cells. Existing regulations did not address it and so it was possible that a new regulatory framework might need to come into force one day.

An industry perspective on pre-clinical studies: Dr Lorenz Mayr (Astra Zeneca R&D)

Dr Mayr began by introducing the AstraZeneca (AZ) Innovative Medicines and Early Development Group, a pre-clinical unit which aims to bring targets forward to the clinic for study. AZ started to work on CRISPR/Cas-9 in a pre-clinical capacity in 2012. The Company has collected genome data on more than 500,000 patients – and much of this data still needs to be translated. Some of the work of the Innovative Medicines and Early Development Group is done in close collaboration with academic centres. The main focus of the unit is on:

- In vitro target validation (using CRISPR technology)
- In vivo animal models of disease
- Genome targeting-based drug discovery.

Dr Mayr emphasised that AZ is not running any human gene editing-based clinical studies, and instead is focusing on its use in pre-clinical work to further address safety and efficiency issues. In the meantime, the company believed that more evidence did need to be collected in relevant pre-clinical animal models, and that much more work needed to be carried out on effective delivery systems.

The Research Funder's perspective: Katherine Littler (Wellcome)

Wellcome (previously The Wellcome Trust) considers that many potential benefits could arise in the future from work being done now on human genome editing. In 2015 the Trust

issued an initial public statement[6] on these potential benefits, whilst making the case that at this stage in the development of governance systems nothing should really "be ruled out or ruled in." The statement will remain under review as new developments emerge. The Trust does agree that human germline genome editing shouldn't take place at present; there is a real need to address the current safety aspects associated with such a procedure.

In the meantime, Wellcome, in its capacity as one of the leading biomedical research funders in the EU, is continuing to encourage researchers to apply to it for funding for research in genome editing. It was also supporting the organisation of meetings, globally, that were helping to move the science, the debates and discussions around genome editing forwards. Communicating about the benefits of genome editing was considered of importance and in that context Wellcome was keen to encourage more public engagement activities on the key ethical and regulatory issues that needed to be addressed. Some of this work on identifying the critical questions to be addressed going forward has thus far been through the work of the Hinxton Group (whose recent meeting on the topic was directly funded by Wellcome) and by the Nuffield Council on Bioethics. Regarding the development of governance models for genome editing, Wellcome's position was that having effective oversight mechanisms in place clearly was important, whether for the regulation of the use of the technique in a research environment or for any eventual "end product." However, whilst recognising the advantages of there being regulatory systems in place, it acknowledged that any one regulatory model was unlikely to be a fit for all. Although it recognised and was supportive of the current UK system of regulation for human genome editing, it was acknowledged that this framework could not necessarily easily be transported to other countries. The national context for regulatory oversight was critical, as there were different norms and beliefs in place, as in the use of embryos, for example. Wellcome supported calls for European regulatory equivalency, not harmonisation, but based on agreed principles.

The patient perspective: Dr Cor Oosterwijk (EGAN)

The European patient community fully supports innovation in genome modifying techniques that will speed up basic and clinical medical research. It was considered however that, since the safety of medical interventions in this field is already sufficiently covered by existing other laws and regulations, moratoria on germline editing as they exist in several countries are in fact superfluous and should therefore come to an end.

There is a need to distinguish between the prohibition of human germline applications because of real safety risks or possible adverse outcomes, from an opposition based on moral, ethical or religious reasons. Of course, patients also want medical interventions to be safe (whether it concerns themselves or their offspring) but most ethical committees, passing judgement on such matters, do not really balance the possible risks of the intervention against the burden of disease, or against the certainty that if nothing is done, suffering and the transmission of the conditions to the next generations will continue. Part of the reason for this, Dr Oosterwijk suggested, is that the perspective of the patient is rarely represented in such ethical committees. The key debate should be focused on the lives of patients, not the direction of research. "Nothing about patients, without patients" should be the driving principle of all ethical considerations.

In addition to the actual burden of the disease, many patients suffer from the additional psychological burden of passing on their disorder to their children and future generations. For almost all of the 6,000 recognised single gene disorders (affecting 5% of the European population) there is currently no cure or effective medical treatment. When societies do not allow available innovation and genetic interventions to be used to prevent the continuation of these disabling genetic disorders, governments and policy makers are not really considering this burden for their citizens and patients. Putting a ban on germline editing also

[6] https://wellcome.ac.uk/sites/default/files/wtp059707.pdf

suggests that governments do not trust themselves to being able to establish appropriate governance structures to regulate germline editing.

It was felt important that the debate should stay away from "black and white" discussions and from the use of terminology as "eugenics" or "scientists playing as God". The debate needed to be more focussed on whether or not society is willing to respect the right for autonomous, informed decision-making on issues of reproduction.

EGAN, the European Patients' Network for Medical Research and Heath, does respect the status of the human embryo, and also respects those people and governments who consider that the embryo deserves absolute protection. However, it goes against moral values to impose one's own ethical convictions on others, limiting them in their choices that will affect their lives. Therefore, it would be difficult to respect regulations that limit the freedom of choice of other countries, and neither the EU nor individual Member States should seek to do so.

It was noted that the EU regulatory landscape for pre-implantation genetic diagnosis (PGD) is just as diverse as for germline gene editing. It was suggested that those people who reject PGD on ethical grounds should then also not object to the gene editing of embryos, for no human embryos would need to be destroyed using this technique. It was also suggested that that those people who consider that the status of the embryo deserves full protection, but do not object to the use of genetic therapies in children, should then also not object also to its application in embryos and foetuses.

Finally, it seems unethical that the current germline debate is completely isolated from the urgent need for pre-conception education and pre-conception care programmes as an integral part of national health care systems, aiming at information on how to prevent genetic disorders and how to contribute to healthy pregnancies, to reduce maternal and childhood mortality and morbidity.[7]

The Public Perception "Bringing the People Back In": Professor Jennifer Merchant (Université Pantheon –Assas Paris II).

Most modern democratic countries have been looking for ways to improve and increase the participation of its citizens in the establishment of new regulatory systems for novel biotechnologies. Two recent examples of such initiatives are those that were established in France and in the United Kingdom. Both countries have top-down regulatory systems, but have different ways of soliciting participation from the public.

In France prior to the 2009 revision of the French Bioethics Law (FBL) the then President Sarkozy, launched the first General Public Discussion, a hybrid consultation process that produced several institutional reports, an interactive internet site, organised debates within regional ethics committees and three Consensus Committees, meetings of which took place in different cities and which focussed on one or two key issues. For each Consensus Conference a representative sample of 25 citizens was chosen by an opinion poll. At the end of the process each of the three groups of citizens drafted a list of recommendations which were then turned into a final report by a government-mandated philosopher.

In the UK there was a public consultation exercise run by the HFEA in 2012 on a number of questions concerning the ethical issues raised by mitochondrial transfer techniques.[8] The Human Fertilisation and Embryology Authority (HEFA) organised *inter alia* a number of public workshops and debates and also set up interactive internet sites to seek views on whether

[7] http://www.who.int/maternal_child_adolescent/documents/concensus_preconception_care/en/

[8] http://www.hfea.gov.uk/9359.html

mitochondrial transfer clinical treatment should be permitted in the UK. A wide range of organisations were consulted on this matter including patient groups, research funders, professional bodies, genetic interest groups as well as faith and community organisations.

In the light of both the French and UK experiments in public consultation, it was argued by Professor Merchant that some form of public consultation on the regulation of CRISPR-Cas9 technology was now required. Such a consultative process could be made more inclusive and meaningful using the current technological resources available today.

Final Discussion Section

Chair: Professor Ernst-Ludwig Winnaker

Clarification was sought (from a US-based delegate) on whether there was (or should be) in place in the EU a system for an abbreviated period of testing before regulatory approval was given? It was pointed out by the Panel that there was a Conditional Approval process in place for rare disease therapy, which could be applied to genome editing, if it were classified as a medicinal product. Concern was raised by the Regulatory bodies present that there really was a need for clinical data from genome editing studies to be validated. If researchers didn't go through the normal process, then it would be difficult for regulators to consider the results of such studies as correct data. The use of "compassionate use" approval was likely to be different at each country level. It was suggested that more attention should be given to the use of registries in carrying out such studies. Some Member States and the EU had invested heavily in the development of registries in their support of new approaches to clinical research.

The real influence of public debate on improving legislation was questioned. The possible downside of some aspects of increased public engagement on regulatory matters had been seen in the use of Citizen's Initiatives in the EU, through which some groups had sought to ban stem cell research and the use of animals in research.

The difficulties in establishing a harmonised approach to the regulation of genome editing research was discussed and acknowledged. The current focus on the restrictions on embryo use, which varied considerably across the EU (and globally), made it unlikely that a common denominator could be found at present. (It was noted however that embryo use was only one element of the wider genome editing landscape.) It was accepted that the importance of patient engagement had been overlooked up to now in attempts to bring about positive changes to the regulatory framework.

There was some agreement that there were greater opportunities for the further promotion of somatic cell-based gene therapy within the EU, and that more should be done to harmonise clinical trials using such an approach. The possible need for a regulatory roadmap was suggested, to guide researchers on the way forward. Concern was raised however on asking only the regulators to identify the specific requirements needed for the assessment of the science and safety of these future therapeutic approaches. There was a need for effective ongoing dialogue between researchers (academic- and commercially-focussed), patients and regulators. It was to be hoped that a flexible regulatory approval system would be in place as more of such innovative interventions move closer to the clinic.

Programme

8:30-9:30 Arrival and registration
9:00-9:15 Welcome and introduction
Professor Pierre Jouannet, French Academy of Medicine, France
Professor Bernard Charpentier, President, FEAM

Session 1: EU Content

Chair: Professor Bernard Charpentier, President, FEAM

9:15-9:35 The perspective of the European Commission
Dr Charles Kessler, Principal Scientific Officer, DG Research & Innovation, Health E5, European Commission

9:35-9:45 Questions & discussion

Session 2: Research – current state, opportunities and regulation

Chair: Professor Virginijus Šikšnys, Member of the Scientific Steering Committee

9:45-10:10 Introduction to the science of genome editing and its potential use in research and medicine

Dr Robin Lovell-Badge, Group Leader and Head of the Division of Stem Cell Biology and Developmental Genetics, Francis Crick Institute, UK

10:10-11:10 Exploring different perspectives on using genome editing for basic research in the EU

Panel discussion to:

- Establish the current state of the regulation of human genome editing uses in basic research in a number of EU countries (and related aspects such as access and storage of human embryos)
- Identify any significant areas where research regulation particularly differs between the EU countries
- Encourage identification of future possibilities of research using genome editing techniques and areas where regulation or concerns might (or have) unnecessarily impeded on research.

Panel members:

- Ruth Mampuys,Coordinator Ethics and Societal Aspects at the Netherlands Commission on Genetic Modification (COGEM)
- Professor Ernst-Ludwig Winnacker, Ludwigs-Maximilians-Universität München, Genzentrum, Germany
- Dr Robin Lovell-Badge, Group Leader and Head of the Division of Stem Cell Biology and Developmental Genetics, Francis Crick Institute, UK
- Professor Giuseppe Testa, Professor of Molecular Biology and Director, Laboratory of Stem Cell Epigenetics, European Institute of Oncology and European School of Molecular Medicine, Italy

11:10 - 11:35 Refreshments

Session 3: Clinical research and applications in human somatic cells – current state, opportunities sand regulation

Chair: Professor Luigi Naldini, Member of the scientific steering committee

11:35 - 11:45 Professor Naldini will introduce the current state of clinical research and potential applications of genome editing in human somatic cells.

11:45 - 12:30 **Exploring different perspectives on genome editing in human somatic cells in the EU**

Panel discussion to:

- Establish the current regulatory landscape for research and applications in a number of EU countries, focusing on regulations around gene therapy and whether these are appropriate for genome editing, and note any areas of variation among Member States.
- Identify any significant areas where research regulation particularly differs between the EU countries
- Encourage identification of future possibilities of research using genome editing techniques and areas where regulation or concerns might (or have) unnecessarily impeded on research.

Panel members:

- Professor Nathalie Cartier-Lacave, Director of Research, INSERM and President, European Society of Gene and Cell Therapy, France
- Professor José M García Sagredo, Professor of Clinical Genetics, University of Alcala and Member of the Spanish Royal Academy of Medicine
- Dr Verónica Martínez-Ocaña, Scientific Officer, Ethics Sector, European Research Council

12:30 - 13:20 **Lunch**

Session 4: Clinical research and applications for germline cells – current state, opportunities, challenges and regulation

Chair: Dr Robin Lovell-Badge, Co-Chair of the scientific steering committee

13:20-13:30 Professor Pierre Jouannet, Co-Chair of the scientific steering committee, will introduce the current state of clinical research and potential applications of genome editing in germline cells.

13:30-13:45 Exploring different perspectives on genome editing in germline cells in the EU

Panel discussion to:

- Establish the current regulatory landscape for research and applications in a number of EU countries.
- Identify any significant areas where research regulation particularly differs between the EU countries or where countries have ambiguous laws/guidelines, and consider the implications of such instances.
- Encourage identification of future possibilities where regulation or concerns might impede research or applications.

Panel members:

- Professor Bernard Baertschi, Institute for Biomedical Ethics, University of Geneva, Switzerland

- Dr Peter Mills, Assistant Director, Nuffield Council on Bioethics, UK
- Professor Pierre Jouannet, French Academy of Medicine, France
- Dr Anna Veiga, Director, Stem Cell Bank, Center of Regenerative Medicine, Barcelona, Spain
- Professor Ewa Bartnik, Professor of Molecular Biology and Human Genetics, University of Warsaw, Poland

Session 5: Cross-sector discussion of human genome editing

Chair: Professor Ernst-Ludwig Winnacker, Member of the scientific steering committee

15:00-16:00 **Roundtable panel discussion to consider various perspectives on the research into, and applications of, genome editing in humans**

- **Regulatory perspective** (EMA): Dr Nicolas Ferry, Member of the Committee for Advanced Therapies, European Medicines Agency and Director of ANSM (French Medicinal Products Regulatory Agency)
- **Preclinical Industry perspective**: Dr Lorenz Mayr, VP Discovery, Innovative Medicines and Early Development, Astra Zeneca
- **Research funder perspective**: Katherine Littler, Senior Policy Adviser, Wellcome
- **Patient perspective**: Dr Cor Oosterwijk, Secretary-general, The Patients Network for Medical Research and Health (EGAN)
- **Public perspective**: Professor Jennifer Merchant, Faculty of Law, Université Panthéon-Assas Paris II, France

Conclusions and next steps

Chairs: Dr Robin Lovell-Badge and Professor Pierre Jouannet

16:00-16:30 An open discussion to consider next steps for human genome editing in the EU. One aspect of the discussion may be to consider the need, or not, for a European framework– and the most pertinent considerations that would need to underpin any such document.

16:00-16:30 **End**

Participant list

- **Professor Monique Adolphe**, French Academy of Medicine
- **Professor Jean-François Allilaire**, French Academy of Medicine
- **Professor Nicholas Anagnou**, Professor of Biology and Group Leader, University of Athens and Biomedical Research Foundation of the Academy of Athens, Greece
- **Professor Raymond Ardaillou**, French Academy of Medicine
- **Samuel Arrabal**, Agence de Biomédecine, France
- **Professor Bernard Baertschi**, Institute for Biomedical Ethics, University of Geneva, Switzerland
- **Professor Ewa Bartnik,** Professor of Molecular Biology and Human Genetics, University of Warsaw and Institute of Biochemistry and Biophysics, Polish Academy of Sciences, Poland
- **Professor Etienne Emile Baulieu**, Université Paris XI-Bicêtre, French Academy of Medicine
- **Professor Pierre Bégu**é, French Academy of Medicine
- **David Beier**, Managing Director, Bay City Capital, California, USA
- **Professor Jean-Michel Besnier**, Université Paris-La Sorbonne, France
- **Dr Ben Bleasdale**, Policy Officer, Academy of Medical Sciences, UK
- **Elizabeth Bohm**, Senior Policy Adviser, Royal Society, UK
- **Daniel Bokobza**, Office parlementaire d'évaluation des choix scientifiques et techniques (OPECST), France
- **Dr Katherine Bowman**, Senior Program Officer, National Academy of Sciences, USA
- **Dr Virginie Bros-Facer**, Research Infrastructure Project Manager, The European Organisation for Rare Diseases (EURORDIS)
- **Dorothée Browaeys**, Journalist, Up Magazine, France
- **Dr Rachel Brown**, Policy Officer, Academy of Medical Sciences, UK
- **Dr Anne Cambon-Thomson**, Société Française de Génétique Humaine, France
- **Professor Nathalie Cartier-Lacave**, Director of Research, Institut national de la santé et de la recherche médicale (INSERM), France; President, European Society of Gene and Cell Therapy
- **Mathias Champion**, Journalist, Le Magazine de La Santé, France
- **Professor Alta Charo**, Warren P. Knowles Professor of Law and Bioethics, University of Wisconsin–Madison, USA
- **Professor Bernard Charpentier**, President, Federation of European Academies of Medicine (FEAM), Belgium
- **Professor Jacqueline Chin**, Associate Professor, Centre for Biomedical Ethics, Yong Loo Lin School of Medicine, National University of Singapore
- **Professor Ellen Clayton**, Professor of Paediatrics and Professor of Law, Vanderbilt University Medical Center; Co-Founder, Center for Biomedical Ethics and Society, Vanderbilt University, USA

Kindly supported by:

- **Dr Barry Coller**, Vice President for Medical Affairs, Allen and Frances Adler Laboratory of Blood and Vascular Biology, Rockefeller University, USA
- **Dr Paul Colville-Nash**, Regenerative Medicine Programme Manager, Medical Research Council, UK
- **Dr Laure Coulombel**, Comité Consultatif National d'Ethique, France
- **Professor Daniel Couturier**, French Academy of Medicine
- **Petra De Sutter**, Committee in Social Affairs, Health and Sustainable Development of the Parliamentary Assembly of the Council of Europe
- **Professor John De Vos**, Institut national de la santé et de la recherche médicale (INSERM), France

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- **Professor John Evans**, Department of Sociology, University of California, USA
- **Professor Anne Fagot-Largeault**, French Academy of Sciences
- **Dr Roy Farquharson**, Chair Elect, European Society of Human Reproduction and Embryology (ESHRE)
- **Professor Marc Fellous**, Institut national de la santé et de la recherche médicale (INSERM), France
- **Dr Nicolas Ferry**, Member of the Committee for Advanced Therapies, European Medicines Agency; Director of ANSM (French Medicinal Products Regulatory Agency)
- **Professor Bärbel Friedrich**, Academic Director, Alfried Krupp Wissenschaftskolleg, Germany
- **Dr Johannes Fritsch**, Scientific Officer, Presidential Office, The German National Academy of Sciences Leopoldina
- **Molly Galvin**, Press Officer, National Academy of Medicine, USA
- **Professor José García-Sagredo**, Professor of Clinical Genetics, University of Alcala; Member, Spanish Royal Academy of Medicine
- **Professor Patrick Gaudray**, Comité Consultatif National d'Ethique, France
- **Manual Gea**, Journalist, Adebiotech, France
- **Vincent Glavieux**, Journalist, La Recherche, France
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- **Professor George Griffin**, Foreign Secretary, Academy of Medical Sciences, UK
- **Marie-France Hanseler,** French Academy of Medicine
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- **Professor Richard Hynes**, Professor for Cancer Research, Koch Institute for Integrative Cancer Research, Massachusetts Institute of Technology, USA
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- **Professor Rudolf Jaenisch**, Professor of Biology, Whitehead Institute for Biomedical Research, Massachusetts Institute of Technology, USA
- **Professor Pierre Jouannet**, French Academy of Medicine; Co-Chair of FEAM scientific steering committee on genome editing
- **Professor Jeffrey Kahn**, Robert Henry Levi and Ryda Hecht Levi Professor of Bioethics and Public Policy, Berman Institute of Bioethics, Johns Hopkins University, USA
- **Dr Charles Kessler**, Principal Scientific Officer, DG Research & Innovation, Health E5, European Commission
- **Dr Jeff Kipling**, Scientific Adviser, Federation of European Academies of Medicine (FEAM)
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- **Marine Lamoureux**, Journalist, La Croix, France
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- **Dr Rebecca Lumsden**, Head of Science Policy, The Association of the British Pharmaceutical Industry (ABPI), UK
- **Alison MacEwen**, Senior Science & Innovation Adviser, British Embassy in Paris, France
- **Ruth Mampuys**, Coordinator Ethics and Societal Aspects, Netherlands Commission on Genetic Modification (COGEM)
- **Professor Gary Marchant**, Faculty Director and Faculty Fellow, Center for Law, Science & Innovation, Arizona State University, USA
- **Dr Verónica Martínez-Ocaña**, Scientific Officer, Ethics Sector, European Research Council (ERC)
- **Professor Jean-François Mattei**, French Academy of Medicine
- **Dr Lorenz Mayr**, Vice-President and Global Head, Reagents and Assay Development, AstraZeneca, UK/Sweden
- **Anna McKie**, News Reporter, Research Fortnight, UK
- **Professor Jennifer Merchant**, Faculty of Law, Université Panthéon-Assas Paris II, France
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- **Dr Peter Mills**, Assistant Director, Nuffield Council on Bioethics, UK; UK Representative on the Council of Europe's Committee on Bioethics
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- **Dr Joana Namorado**, DG Research & Innovation, Ethics E1, European Commission
- **Dr Cor Oosterwijk**, Secretary-General, The Patients Network for Medical Research and Health (EGAN); Director, National Patient Alliance for Rare and Genetic Disorders (VSOP)
- **Gemma Ortiz Genovese**, Consultant, Médecins Sans Frontières/Doctors Without Borders (MSF)
- **Professor Jean-Christophe Pages**, Haut Conseil aux Biothechnologies, France
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- **Professor Jochen Taupitz**, Managing Director, Institute for German, European and International Medical Law, Public Health Law and Bioethics of the Universities of Heidelberg and Mannheim
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- **Bethan Wolfenden**, Bento Bio, UK
- **Camille Yaouanc**, Reporter, Gènéthique

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French Academy of Medicine
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Irish Academy of Medical Sciences
Italian Academy of Medicine
Lithuanian Academy of Sciences
Portuguese Academy of Medicine
Romanian Academy of Medical Sciences
Spanish Royal National Academy of Medicine
Swiss Academy of Medical Sciences
Royal Netherlands Academy of Arts and Sciences
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