

# The promise of human genome editing for rare and genetic disease

**Summary report of the 2019 FORUM  
Annual Lecture**

## **The Academy of Medical Sciences**

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# Executive summary

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**Genome editing is a disruptive technology that is empowering biomedical research and set to transform medicine. This important tool is expanding the range of treatments available and our understanding of the genetic code. The technology is advancing at a fast pace and yet its capabilities have only started to be explored.**

The Academy's 17<sup>th</sup> FORUM Annual Lecture, held on 5 September 2019, brought together a range of experts to discuss the promise of human genome editing for rare and genetic diseases. John Leonard M.D., President and Chief Executive Officer of Intellia Therapeutics, described his company's pioneering work developing a pipeline of genome editing treatments for severe and life-threatening diseases. The meeting also explored the opportunities of genome editing for preclinical research, the ethical implications of research and therapies using the technology, and the importance of active public and patient engagement.

*"We may be nearing the beginning of the end of genetic diseases."*

Professor Jennifer Doudna, Professor of Chemistry & Molecular and Cell Biology at University of California and Co-Founder Intellia Therapeutics

Collectively, rare diseases are not rare. Around six percent of the population suffer from a rare disease at some point in their lives. This translates to around 3.5 million people in the UK. Many of these conditions may be treated by addressing their genetic drivers as 80% of rare diseases have a genetic component. Four elements are needed for genome editing technology to be applied: a 'tractable' disease, a known causative gene, a targetable tissue and an appropriate editing tool. Broadly, there are two ways of using genome editing for therapy: by 'fixing the broken gene' *in vivo* in disorders with a genetic component, or by 'rewiring and redirecting' normal cells *ex vivo* for disorders of altered function such as autoimmune diseases and cancer.

It was clear from the discussion that:

- Genome editing therapies are **near to entering the clinic**. The current research focus is on diseases caused by a modification in a single gene (also known as monogenic diseases), advanced cancers and autoimmune diseases, but this list is set to expand.
- The growing genome editing toolkit presents **opportunities for life-saving research**, including in drug target discovery and disease biology.
- There is a **need for a robust and fair regulatory model**, which considers the risks and benefits of genome editing based therapies and the challenges of rare disease clinical trials.

- **The patient and public voice** is important to ensure science remains trustworthy and to respond to their needs and concerns, including around timescales, accessibility and accountability.
- There are wide-ranging **ethical implications** surrounding genome editing, particularly in the germline, and there is a need for governance of science on a global scale.

## 2019 FORUM Annual Lecture

The keynote lecture was given by **John Leonard M.D.**, Chief Executive Officer of Intellia Therapeutics. This was followed by a panel discussion chaired by Professor Sir Robert Lechler PMedSci, President of the Academy of Medical Sciences.

Dr Leonard was joined by four guests who further explored the academic, industry, and patient perspectives of human genome editing:

- **Dr Mathew Garnett**, Group Leader, Wellcome Sanger Institute
- **Dr Nicola McCarthy**, Business Unit Manager, Horizon Discovery
- **Dr Alison Kay**, Patient representative
- **Dr Sarah Chan**, Chancellor's Fellow, University of Edinburgh

The key points of discussion from both the lecture and subsequent debate are summarised in this meeting report. A video recording of this event is also available on the Academy's website.<sup>1</sup>

This meeting was convened as part of the Academy's FORUM programme, which was established in 2003 to recognise the role of industry in medical research and to catalyse connections across industry, academia and the NHS. We are grateful for the support provided by the members of this programme and are keen to encourage more organisations to take part. If you would like information on the benefits of becoming a FORUM member, please contact [FORUM@acmedsci.ac.uk](mailto:FORUM@acmedsci.ac.uk).

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<sup>1</sup> <https://acmedsci.ac.uk/more/events/2019-forum-annual-lecture>

# An introduction to genome editing

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**Genome editing is not a new technology. Scientists have been editing the DNA of organisms for many decades. However, it is only in the last ten years, with the discovery and development of the CRISPR-Cas technology, that genome editing has become simple, scalable and selective. This has led to wide and rapid adoption in laboratories across the world.**

Researchers first discovered clustered repeating DNA segments, termed CRISPR (Clustered Regularly Interspaced Palindromic Repeats), in bacteria in the 1980s.<sup>2</sup> It took over a decade for these repeats to be identified as part of a bacterial adaptive defence system. CRISPR sequences were found to contain viral DNA, which was used to guide a DNA-cutting enzyme, termed Cas, towards attacking viruses.

Scientists co-opted this mechanism to create a precise and programmable tool for editing the genome.<sup>3</sup> The CRISPR-Cas system uses the Cas enzyme as 'molecular scissors' to specifically cut DNA at any point within the genome based on a guide RNA. Researchers can remove or insert DNA sequences and make very precise individual changes in the DNA sequence. This can now be done more rapidly, more efficiently, and on a larger scale than any previous genome editing tools allowed.

While CRISPR-Cas technology led to the expansion of genome editing research, new techniques are now being developed that could provide advantages over the CRISPR-Cas system. This could be through new versions of CRISPR-Cas that improve specificity or reduce the number of double strand breaks, or through an entirely new natural or synthetic enzyme system.

The genome editing toolkit is rapidly growing, as are the number of potential applications. Scientists are using genome editing to probe human biology and it is now making its way from the laboratory into the clinic.

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<sup>2</sup> Ishino Y, et al. (1987). *Nucleotide sequence of the iap gene, responsible for alkaline phosphatase isozyme conversion in Escherichia coli, and identification of the gene product.* Journal of Bacteriology **169**, 5429–5433.

<sup>3</sup> Jinek M, et al. (2012). *A programmable dual-RNA-guided DNA endonuclease in adaptive bacterial immunity.* Science **337**, 816–821.

## What is the difference between somatic and heritable genome editing?

**Somatic genome editing** is done in cells that are not involved in reproduction and therefore changes are not heritable. The risks associated with this type of research and therapeutic applications are lower, although not negligible. Today, this represents the major use of genome editing in research.

**Heritable or germline genome editing** involves altering the cells involved in reproduction, such as the egg, resulting in changes which are heritable and so passed on to future generations. There are important ethical considerations regarding the acceptable use for germline genome editing as a therapy. There are possible unintended short and long term effects of heritable genome editing, both for the individual, and for society as a whole.

# Genome editing: moving to the clinic

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**Genome editing is now on the cusp of transforming the lives of patients. It is being applied to treatments or cures for a number of rare diseases. Over 300 million patients are affected by rare diseases worldwide and many have no or limited treatment options available. Intellia Therapeutics is one of several companies pioneering the clinical development of genome editing therapies for rare and genetic-based diseases. The meeting explored the future of genome editing therapies.**

## Rare and genetic diseases

### The burden of rare and genetic diseases

A rare disease is defined by the European Union as one that affects less than 1 in 2,000 people. In the UK, a single rare disease can affect up to 30,000 people, but the majority will affect far fewer. Rare diseases are infrequent individually, but together are prevalent: 1 in 17 people, or almost six percent of the population, will be affected by a rare disease at some point in their lives. This equates to approximately 3.5 million people in the UK.<sup>4</sup>

These diseases are often chronic and life-threatening, with the majority having limited or no treatment options. Rare diseases are also expensive to treat, costing the NHS approximately £15 billion per year.<sup>5</sup> Much of this is spent on diagnosis, as reflected in the experience of panellist Dr Alison Kay, who described the challenges of the 'diagnostic odyssey' for her son (see box).

Eighty percent of rare diseases are genetic in nature, caused by one or more abnormalities in the genome.<sup>6</sup> Many of these diseases are caused by alterations in a single gene (also known as monogenic diseases). Some of the most prevalent and well-known monogenic rare diseases include variants of cystic fibrosis and retinitis pigmentosa.

Dr Leonard emphasised that an adaptable universal system aimed at restoring faulty genes would be a great step forward in treating these conditions overall.

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<sup>4</sup> <https://www.raredisease.org.uk/what-is-a-rare-disease/>

<sup>5</sup> Genetic Alliance UK (2016). *The hidden costs of rare diseases: A feasibility study.*  
[https://www.geneticalliance.org.uk/media/2502/hidden-costs-full-report\\_21916-v2-1.pdf](https://www.geneticalliance.org.uk/media/2502/hidden-costs-full-report_21916-v2-1.pdf)

<sup>6</sup> <https://www.raredisease.org.uk/what-is-a-rare-disease/>



## The diagnostic odyssey

Dr Alison Kay shared her experience as a parent of a child with a rare condition. Dr Kay described her eight-year old son, Bertie, who has a form of muscular dystrophy, a muscle weakness disease. Bertie is one of the ~70,000 people living with muscular dystrophy in the UK and, under this umbrella term, there are over 60 different forms of the disease. Muscle weakness conditions can have a range of severity and can affect people in a myriad of ways, including mobility, cardiac and respiratory issues.

Bertie has a rare child-onset condition called Ulrich's Congenital Muscular Dystrophy.

He is semi-ambulant, able to walk a short distance on a flat surface but unable to climb stairs or run around in the playground.

Dr Kay highlighted the challenges of getting a diagnosis for such a rare disease.



*"We went on the diagnostic odyssey... These conditions are very rare and very complicated; it's not as simple as ordering a genetic test. You often have to wait for a special study to be happening."*

There is presently no cure for muscular dystrophy. Commenting on genome editing, Dr Kay described the hope and the disappointment around the development of new therapies.

*"The neuromuscular community has experienced quite a few false starts. I think false starts are great if they take us somewhere and we learn something but I would say we are cautiously optimistic."*

### What are the criteria for treating a disease using genome editing?

To consider how and when genome editing might be practical, Dr Leonard described four elements to determine whether genome editing may be applied as a therapy:

1. It should be a **tractable condition**, for example chronic, progressive or reversible – where such treatment will have a positive impact on patient outcomes or symptoms.
2. There should be a known **causative gene**. The nature of the genetic problem and how this fits into the overall complex system needs to be known.

3. There should be a **target tissue**, ideally where the causative gene is expressed (and limited to) and is accessible for therapy. Expression of the disordered gene throughout the body makes it very difficult to reach and produce a therapeutic outcome.
4. Finally, there needs to be an appropriate **editing tool** to effect the change needed, for example repair of the gene.

Dr Leonard hopes to extend the list of diseases to which genome editing can be applied. The panel emphasised that preventing progression or even a modest therapeutic outcome can be life-changing, which has implications for how research priorities are set and how these can be aligned with patient need.

## Genome editing as a therapy

Broadly, there are two ways of using genome editing for therapy: by 'fixing the broken gene' in disorders with a genetic component, or by 'rewiring and redirecting' normal cells for disorders of altered function such as autoimmune diseases. The way genome editing is applied is different in each of these methods: in the first instance, CRISPR-Cas is deployed *in vivo* and is used as a therapy, like a pharmaceutical drug, to correct the faulty gene *in situ*; in the second, CRISPR-Cas is used to create the therapy by modifying healthy patient cells *ex vivo*, which are later put back into the patient.

### 'Fixing the broken gene'

There are three archetypal edits that can be made to DNA to try to effect change: a **knock out**, which involves inactivation or deletion of the disease-causing DNA sequence; **repair**, where the 'misspelled' disease-driving DNA sequence is corrected; or an **insertion**, where a new DNA sequence is inserted in the genome to produce a therapeutic protein. The type of edit used will be dependent on the disease-causing element.

For diseases that result from of a single genetic change, genome editing can be used as a therapy to 'fix' the disease-causing sequence using one of the three archetypal edits. The liver contains several addressable genetic disorders where the condition is tractable and isolated to known causative genes expressed almost exclusively in this organ. The liver is also easy to access using lipid nanoparticles. Dr Leonard gave two pre-clinical examples Intellia Therapeutics is currently working on where CRISPR-Cas RNA machinery coated in lipid nanoparticles is delivered intravenously as a therapy to target disease-causing DNA sequences.

#### *Transthyretin Amyloidosis (ATTR)*

ATTR is a progressive, multi-systemic and life-threatening disease. Worldwide prevalence of ATTR has been estimated at 50,000 people. Hereditary ATTR is caused by the accumulation of a misfolded blood protein called transthyretin (TTR), which is primarily synthesised and secreted by the liver.<sup>7,8</sup>

While there are over 120 known mutations which can cause ATTR, Dr Leonard described how disabling the TTR gene in hepatocytes treats all of these mutations. Intellia Therapeutics have conducted pre-clinical studies using a knock-out approach to interrupt the TTR gene sequence. A single dose of CRISPR-Cas targeted at the TTR gene in non-human primates

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<sup>7</sup> <https://www.nhs.uk/conditions/amyloidosis/>

<sup>8</sup> Hawkins PN, *et al.* (2015) *Evolving landscape in the management of transthyretin amyloidosis*. *Annals of Medicine* **47**, 625–638.

resulted in a 95% reduction in circulating TTR protein that was sustained for at least six months. This observation period is ongoing (currently at 10 months) and Dr Leonard expected this TTR reduction to be permanent. Dr Leonard expects Intellia to submit to regulatory bodies mid-2020 to begin human clinical trials.

### *Haemophilia B*

Haemophilia B is a blood-clotting disorder, with severe cases often having painful spontaneous bleeding into joints. It is a rare genetic disorder caused by missing or defective Factor IX - a blood-clotting protein encoded by the F9 gene.

Patients with haemophilia B are treated chronically with replacement Factor IX. Introduction of the F9 gene into the liver may reduce the need for replacement Factor IX therapy or potentially even act as a cure. This editing process requires both a DNA break and insertion of a template of Factor IX.

In pre-clinical experiments in non-human primates, within two weeks of supplying CRISPR-Cas machinery with the DNA template, normal levels of the Factor IX protein can be detected in the plasma. Dr Leonard explained that this effect should be permanent and so could be applicable to young children.

## **Rewiring and redirecting cells**

The 'rewire and redirect' method uses the same principles and editing tools to modify normal cells to introduce a new functionality. This is used for diseases of 'altered function' such as immune disorders and cancer. Healthy cells are taken from patients and their DNA is modified to give the cells a new function.

### *Acute Myeloid Leukaemia (AML)*

AML is a cancer of the blood and the most common type of acute leukaemia in adults, with around 3,100 new cases diagnosed each year in the UK. AML progresses rapidly and typically requires immediate treatment. Overall five-year survival rates for patients with AML is less than 30%.<sup>9,10</sup> Despite the complex genetics of AML, the disease can be considered a failure of the immune system to recognise cancerous cells and kill them. T cells are a type of lymphocyte, which have the ability to directly kill cells recognised as a threat – for example virus-infected cells. Replacing the T cell receptor (TCR) of a patient's T cells to one that can recognise a tumour cell arms them with the ability to recognise and attack cancerous cells. In collaboration with Ospedale San Raffaele (a university hospital in Milan), Intellia Therapeutics demonstrated that cells with modified TCRs were able to kill patient-derived AML cells. Dr Leonard noted that if this result is replicated in patients, it could potentially be a powerful and effective tool to deal with a currently poorly treated cancer.

## **The road ahead**

In the current clinical landscape, animal cells can be edited in selected tissues *in vivo* and complex cell systems, such as the immune response, can be modified. Looking ahead, Dr Leonard highlighted multiple programmes taking place across genome editing companies that are now entering clinical phases of research. He expected the first human data to be available by the end of 2019 and anticipated that CRISPR-Cas therapies would be on the market in the next few years.

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<sup>9</sup> <https://www.nhs.uk/conditions/acute-myeloid-leukaemia/>

<sup>10</sup> <https://seer.cancer.gov/statfacts/html/amyl.html>

Dr Leonard also recognised the role of fundamental academic research in this area, which feeds into the clinical research being done by companies such as Intellia. Future research will focus on expanding the list of addressable diseases through investigating approaches to reach more tissues, for example by using specific receptors to guide the CRISPR-Cas machinery to specific cells or tissue. Dr Leonard predicted that in the next 20 years, there will be a whole host of tissues accessible for genome editing with new delivery mechanisms. Another research priority will be to expand our knowledge of disease genetics.

While genome editing has a range of medical uses, Dr Leonard did not see it displacing effective and less expensive therapies. He believed the focus should be on 'undruggable', severe genetic disorders, immune disorders and advanced cancers.

The applicability of genome editing as a therapy beyond these diseases was addressed in the panel discussion. Dr Leonard described moving beyond these initial conditions as a stepwise process. Within monogenic disorders, there can be a spectrum of phenotypes with different manifestations of the disease. There needs to be a strong link between the phenotype and underlying causative gene – any additional modifiers or complications would make the disease more difficult to treat using genome editing. Applications for chromosomal disorders were noted as very challenging and it is not clear at present how CRISPR-Cas could be harnessed in such conditions.

Many common diseases are polygenic, involving multiple genes. A CRISPR-Cas therapy for such diseases would require an in-depth knowledge of how different alterations in the genome relate to cause the disease phenotype. An additional difficulty for polygenic diseases comes from changes in DNA often occurring in the space in-between genes. These non-coding regions are poorly understood but play a key role in influencing gene expression.

The effect of the environment also complicates CRISPR-Cas therapy for polygenic disease. Some conditions are not associated with genetic alterations but rather epigenetic alterations. For example, the effect of stress can cause changes in epigenetics, which persist between generations.<sup>11</sup> With CRISPR-Cas, tools are available to make epigenetic changes to DNA, which could potentially be applied in future once there is a better understanding of disease-causing epigenetic changes.

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<sup>11</sup> Dickson DA, et al. (2018). *Reduced levels of miRNAs 449 and 34 in sperm of mice and men exposed to early life stress*. *Translational Psychiatry* **8**, 101

# Using genome editing in preclinical research

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**Genome editing is being applied as a powerful tool for scientific research, unlocking discoveries about biology and disease. By precisely manipulating DNA, the exact role of genes, and the implications of changes in them, can be uncovered. Scientists are now looking beyond the CRISPR-Cas system to new tools that are even more accurate and easy to use. The panellists discussed the applications of genome editing for understanding fundamental biology and how these findings can be applied to tackle some of the biggest health challenges.**

## Applications of genome editing

While genome editing can be used as a therapy and to create therapies, it began as, and still is, an important research tool. Dr Mathew Garnett (Wellcome Sanger Institute) and Dr Nicola McCarthy (Horizon Discovery) described ways in which researchers in academia and industry are using genome editing to better understand genetic and rare diseases.

### Using genome editing for drug discovery

Finding new disease targets for medicine is time consuming and costly. Dr Garnett described how his lab uses genome editing on cancer cell lines for cancer drug target discovery. In hundreds of different cancer cell lines, his group has individually knocked out every single gene in the human genome and measured the impact on cancer cell survival.<sup>12</sup> This revealed many new drug targets, including a protein named Werner helicase that has subsequently garnered considerable interest from the pharmaceutical industry.

Alongside initial target generation, genome editing screens in cancer cell lines have been found to be a robust way of understanding how drugs work, by knocking out genes in a disease cell line and determining the impact on the drug. A recent study found that a number of drugs in clinical development did not work as expected, with drugs able to kill cancer cells despite the target protein being knocked out.<sup>13</sup> Thorough genetic validation of a drug's proposed mechanism of action prior to clinical trials may be a robust way to predict the therapeutic value of a new drug candidate.

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<sup>12</sup> Behan FM, *et al.* (2019). *Prioritization of cancer therapeutic targets using CRISPR-Cas9 screens.* *Nature* **568** (7753), 511-516

<sup>13</sup> Lin A, *et al.* (2019). *Off-target toxicity is a common mechanism of action of cancer drugs undergoing clinical trials.* *Science Translational Medicine* **11**, eaaw8412.

One of the advantages of genome editing is the ability to look at the effects of genes and their interactions in specific cell populations. An important area of drug discovery is researching how people within a population respond to drugs differently. One well-known example is anaesthetics, where patients can react poorly to drugs due to pinpoint differences within their genome. As genome editing tools evolve, researchers could consider these issues on a cell population level, rather than a patient level.

## Using genome editing to create better disease models

There is a wealth of data about the genetic basis for many diseases. However, given the size of and natural variation in the population's genomes, distinguishing which genetic changes specifically lead to disease, and how, can be difficult. Genome editing is helping to solve this puzzle by allowing scientists to introduce genetic changes into the DNA of cells and to study their effect on proteins, cells, tissues and organisms much more rapidly than was previously possible, accelerating discovery. This is already proving invaluable for the understanding of diseases such as inflammatory bowel disease, cancer and Parkinson's disease, as well as developmental disorders in children.<sup>14</sup> Using genome editing technologies, researchers can also recapitulate the mutations in patients, or screen for regulatory elements, in non-coding regions to understand their role in health and disease.<sup>15</sup>

## Beyond established cell lines

The simplicity of using recent genome editing technologies has opened up new research avenues for genome editing in cell types that were previously difficult – such as primary cells, which are considered to align more closely with patient biology than immortalised cell lines. Dr McCarthy gave the example of performing CRISPR-Cas screens in primary T cells from blood donors. Researchers can determine how the loss of a particular gene impacts the ability of these cells to survive or even work in a particular setting, such as in the immunosuppressed environment of a solid tumour.

In addition, human induced pluripotent stem cells (iPSC) can provide a source of patient-relevant material to study and are particularly useful for disease modelling as they can differentiate into many different cell types. iPSC can be made from patient samples or genome edited to recreate disease-causing mutations. Using iPSC, researchers can study the effect of mutations upon a hierarchy of cell types – including many which would not normally be accessible through patient samples or cell lines.<sup>16</sup>

## CRISPR-Cas beyond genome editing

While originally being utilised as a genome editing technology, the use of CRISPR-Cas has advanced and can be used to downregulate or overexpress genes, without making changes to the DNA code. Manipulating gene expression allows further understanding of gene networks within a particular cell to better inform therapy development.

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<sup>14</sup> Cai L, et al. (2016). *CRISPR-mediated genome editing and human diseases*. *Genes & Diseases* **3(4)**, 244-251

<sup>15</sup> Sanjana NE, et al. (2016). *High-resolution interrogation of functional elements in the noncoding genome*. *Science* **353(6307)**, 1545-1549.

<sup>16</sup> Bassett AR, et al. (2017). *Editing the genome of hiPSC with CRISPR/Cas9: disease models*. *Mammalian Genome* **28(7)**, 348-364.

# Technical challenges of genome editing

## Off-target effects

The panel discussed the accuracy of genome editing technologies and agreed that characterising off-target effects is essential. An off-target effect is defined as a non-specific or unintended genetic modification. Dr Leonard described how when using CRISPR-Cas, off-target effects are primarily down to the choice of RNA guide used to direct the Cas enzyme to a specific region in the genome.

Dr McCarthy highlighted that characterising off-target effects and how they can be mitigated is a large part of research and development at Horizon Discovery. She also added that concerns about the off-target effects of CRISPR-Cas has led to a resurgence of interest in older techniques. For example, shRNA (short hairpin RNA) is a clinically approved established technique, which can silence gene expression – a similar effect to using CRISPR-Cas to knock-out a gene.

## Efficiency of genome editing

Large portions of the genome are packaged away in dense and compact DNA-protein complexes called chromatin. If a gene is being actively transcribed the chromatin will be less densely packed to allow access to the DNA strands. In future, it will be important to better understand the effect of DNA accessibility on the genome editing machinery in different cell types or parts of the genome. Dr Garnett noted that CRISPR-Cas is believed to access densely compacted DNA where it can introduce DNA damage. Much of the data regarding CRISPR-Cas efficiency in different cell lines and parts of the genome is open-source, allowing for mining through AI methods.

# Risk, regulation and society

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**Editing genes to treat human disease has never been easier, but with such progress comes important questions: What are the ethical implications of editing the human genome? How will genome editing be regulated? And how do patients and the public feel about its use?**

In their panel presentations, Dr Sarah Chan (University of Edinburgh) and Dr Alison Kay (patient representative) described some of the societal, ethical and regulatory considerations, as well as challenges for patient communities and society at large when considering somatic human genome editing. Some of these issues will also encompass heritable or germline editing, which will be discussed in the next section.

## Ethical considerations

The ethics of genetic modification has been a topic of discussion for over 40 years. However, recent technological developments have expanded the breadth of its potential impact. Genome editing is now simpler, more precise and requires fewer resources, which dramatically widens the user base with relatively cheap 'DIY CRISPR kits' being readily available online. These developments have accelerated the need for conversations about the acceptability and applicability of human genome editing, and consensus regarding appropriate means of global governance.

### What is acceptable use and acceptable risk?

Some of the most important ethical issues raised by realising the promise of human genome editing relate to global governance of science and managing the science-society relationship. One part of governance is considering how risk is understood, and determining a responsible approach to assessing and managing the risk associated with genome editing. What constitutes an acceptable risk might be specific to the disease. This brings some ethical questions around the distribution of the benefits and burden of participation, particularly for rare diseases or small patient cohorts.

Risk-benefit analysis will be key when considering which conditions genome editing treatment could be applied to. For example, the more severe a disease, the more risk might be accepted in trying to treat or cure it. However, Dr Chan asked: what is meant by 'serious'? What genes count as 'broken'? And at what point does something stop being a disease and start being something that is optional to fix or isn't serious enough?

The answers to these questions may change depending on sociocultural context and values. Members of the public may have different values regarding genome editing, which may be conflicting yet equally valid, known as value pluralism. There is also the effect of sociocultural context when considering risk, harm and what constitutes a disease, for example the effect of social stigma of diseases in a community. Dr Chan highlighted the argument that rather than attempting to eliminate some conditions using current or emerging genetic technologies, we



should instead be promoting acceptance, creating an accessible society and valuing diversity.

On communicating risk, Dr Kay emphasised the importance of patient consent, and for patients and clinicians to truly understand risk, as this can be interpreted differently by different people. For example, a five percent risk may be acceptable to some but not to others. Effective risk communication is critical for informed decision making. Perception of risk can be affected by statistical literacy, patients' health beliefs (including trust in technology) and how risk is communicated.<sup>17</sup> This is particularly important for novel technologies where the technology can be hard to understand and the risks are still being characterised.

## Engaging members of the public and patients

Public and patient involvement throughout the research cycle has expanded in recent years. This can benefit researchers through improved quality and relevance of research or therapies. It also acts as a cornerstone for public accountability and transparency, particularly necessary as most academic research is publicly funded. For scientific topics with potentially widespread impact, public dialogue and consensus is needed. This is difficult as there is not a single 'general public' with one voice and one list of concerns, but diverse publics who will have different views.<sup>18</sup> In this report, the term 'the public' is intended to encompass this diversity of publics with different interests, backgrounds, priorities and concerns.

### The importance of patient voices

Seeking the views of patients and their families from across the patient journey is vital to ensure that priorities across sectors are relevant and meet the expectations of patient communities. As a member of multiple patient panels, Dr Kay outlined several areas of concern for patients around genome editing. She noted the large gaps in understanding across the patient community – particularly whether genome editing therapies would be curative, as discussed below. There are concerns around timescales and accessibility of therapies. The neuromuscular community has seen drug therapies demonstrated to be safe and effective, but later proved inaccessible due to cost or length of time taken to get regulatory approval. She highlighted the large, and ultimately successful, campaign led by patients and charities for the use of the first treatment for Duchenne Muscular Dystrophy, Translarna (ataluren), in the UK.<sup>19</sup> Finally, there are concerns about accountability, including who will decide who has access to genome editing therapies and which conditions they will be used for. Despite these concerns, Dr Kay felt that the neuromuscular community was cautiously optimistic about therapies which involved genome editing.

*"When conditions are extremely rare – sometimes one in a million is quoted for my son – who will make the decision that his cure or his therapy is worth researching?"*

Dr Alison Kay, patient representative

<sup>17</sup> Naik G, et al. (2012). *Communicating risk to patients and the public*. British Journal of General Practice **62(597)**, 213-216

<sup>18</sup> Morrison M, et al. (2019). *CRISPR in context: towards a socially responsible debate on embryo editing*. Palgrave Communications **5**, 110.

<sup>19</sup> <https://www.actionduchenne.org/get-involved/campaign-for-change/the-campaign-for-translarna/>

## How do we engage with patients and members of the public?

Dr Kay highlighted that there are varying levels of understanding of genome editing among members of the public. As such, these conversations should be dealt with carefully. Somatic genome editing is often conflated with that of germline editing, which can lead to important ethical misunderstandings. Dr Kay emphasised that while even a modest patient outcome can be transformative, misunderstanding about whether medicines will be a therapy or curative is still a major issue.

The perception and excitement around technologies, as seen in stem cell therapies for example, can create a 'hope and hype' cycle which drives demand and enthusiasm for treatments. This can lead to support for therapies which may have otherwise not arisen, but overhype can result in exploitation of patients.

*"There's a lot of talk of cures and, when you're needing hope, it is very easy to let the pony out of the stable and run with it."*

Dr Alison Kay, patient representative.

Dr Chan highlighted the importance of responsible discourse in conversations about genome editing. If members of the public are primarily encouraged to think only about the far-future hypothetical scenarios of genome editing, such as human enhancement, they can be misled as to the realities of the science and what it can achieve in the near-present.

The role of the public in the process of science and innovation was also discussed. Members of the public appear to be increasingly unwilling to be passive patients and research subjects, and are seeking a more active role in research participation. In addition, experience with other areas of biomedical technology and medical innovation, particularly stem cells, has demonstrated that the combined forces of patient need, commercial marketing and consumer purchasing power is significant. This can lead to the premature use of these technologies in research and public settings without a sufficient evidence base to justify their use. Regulation needs to pre-empt such a scenario and be proactive in mandating appropriate uses. Ways to harness public enthusiasm and demand in order to promote ethically robust and socially responsible development of genome editing need to be found.

The panel agreed that the UK has considerable experience with large public engagement exercises. This reputation has been built on a number of key experiences – most notably the negative public response to genetically modified crops and the successful implementation of mitochondrial DNA transfer. These experiences demonstrate the importance of early public engagement and of remaining responsive to public concerns. Early engagement with the public in the conversations around human genome editing, on topics such as acceptable and unacceptable uses and what members of the public want and need from this technology, was welcomed as a very positive approach. The Royal Society public dialogue on attitudes to genetic technologies found that there is a lot of enthusiasm and hope around the technology.<sup>20</sup> Concerns were raised with how the technology is shaped and how it can be used going forward to create the type of society that is wanted. Participants stressed that how this information is used and implemented in a meaningful and effective way still needs to be developed.

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<sup>20</sup> <https://royalsociety.org/topics-policy/publications/2018/genetic-technologies-public-dialogue/>

# Regulation and governance

The UK regulatory system is a national strength and perceived internationally as one of the best regulatory models in the world. The most appropriate regulatory and commercial models for genome editing still need to be determined, alongside global scientific governance to maintain public trust.

## Moving to public-engaged global governance

The panel agreed that the UK is proficient at developing evidence-based, proportionate regulation that has been informed by public dialogue and engagement. Dr Chan described the well-established method of public engagement and bioethical policy making that has been established since the Warnock Committee.<sup>21</sup> The current UK system for regulation, for example embryonic research, is seen as the international gold standard.

Participants discussed the importance of proportionate regulation that is acceptable for society and businesses, and that is supported by appropriate resources to oversee and enforce its implementation. There is also a need to be mindful of the effect of transnational regulatory differences. For example, if the UK becomes the hub of innovative medicine, there is a risk of becoming a 'destination' for such treatments, while in the opposite case, the UK risks companies and researchers moving overseas and losing such innovation. Without measured and responsible use of genome editing, particularly germline genome editing, there is a risk of undermining public trust. This in turn could lead to overly stringent regulation and hesitation from investors, which could delay the development of legitimate therapies. Reliable governance and transparent, trustworthy science will be key to enabling genome editing to reach its full potential.

The UK could play a leading role in ethics, regulation and governance at a global level, but consideration will need to be given to the modes of engagement that are effective and appropriate in different regional contexts, and how these can contribute to responsible and ethical governance.

## Navigating the regulatory environment

Genome editing may not fit neatly into the current regulatory landscape for a number of reasons, including complicated benefit-risk analysis and the highly evolved economic model required. The most appropriate regulatory and commercial models to ensure safety, timeliness and accessibility of such therapies are yet to be determined.

The adaptability of genome editing therapy could lead to highly personalised medicine with the potential to design individual disease-causing gene sequences for a single person. However, this would require a new clinical trial paradigm for the rarest disorders as traditional approaches using large randomised controlled trials and conventional commercial incentives do not apply.

Dr Leonard suggested that there may be ways to extrapolate similar work done in larger patient populations. This would require concerted effort across academia, industry and the regulatory sector, with trial design based on extensive pre-clinical work and previous trials

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<sup>21</sup> Committee of inquiry into human fertilisation and embryology (1984). *Report of the committee of inquiry into human fertilisation and embryology*. <https://www.hfea.gov.uk/media/2608/warnock-report-of-the-committee-of-inquiry-into-human-fertilisation-and-embryology-1984.pdf>

using the same genome editing machinery but with a different guiding mechanism. The extrapolation of patient safety and efficacy across diseases would require a thoughtful and robust benefit-risk assessment. For example, more risk may be tolerated for a serious and life-limiting condition or an edit to the genome that will not be inherited. For extremely rare diseases, 'the trial may be the treatment', involving the entire patient population. Highly evolved economic models will need to be developed in parallel. For instance, one-off treatment gene therapies will require a different cost model.

# Heritable genome editing

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**Heritable or germline genome editing results in changes which are passed onto future generations. This could be used to cure genetic disease before birth. However, this raises questions about the technology's acceptability, the level of risk involved, which diseases should be treated, and who decides each of these factors. The panel considered the current environment of heritable genome editing and how a global consensus that is acceptable to the scientific community and, most importantly, wider society is required.**

## The current heritable genome editing landscape

The vast majority of genome editing research in academia and industry is performed in somatic rather than germline cells. In fact, only one researcher in the UK is approved by the HFEA to conduct research using genome editing on embryos.<sup>22</sup> In addition, UK regulations currently limit the culture of embryos in the lab to a maximum of 14 days and it has only been in the last few years that this has been scientifically possible.<sup>23,24</sup>

Until recently, while fundamental research was ongoing for potential future use, heritable genome editing was considered too risky to proceed with clinical use. This was coupled with calls for continued international discussion of potential benefits, risks and oversight of this technology. In November 2018, Dr He Jiankui announced the birth of twin girls whose *CCR5* gene had been edited to attempt to provide immunity against HIV. This received international condemnation for scientific, ethical and moral reasons.<sup>25, 26</sup>

In response, the WHO expert advisory committee on governance and oversight of human genome editing has advised that 'regulatory or ethics authorities refrain from issuing approvals concerning requests for clinical applications for work that involves human germline genome editing'.<sup>27</sup>

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<sup>22</sup> <https://www.hfea.gov.uk/about-us/news-and-press-releases/2016-news-and-press-releases/hfea-approves-licence-application-to-use-gene-editing-in-research/>

<sup>23</sup> Committee of inquiry into human fertilisation and embryology (1984). *Report of the committee of inquiry into human fertilisation and embryology*. <https://www.hfea.gov.uk/media/2608/warnock-report-of-the-committee-of-inquiry-into-human-fertilisation-and-embryology-1984.pdf>

<sup>24</sup> Deglincerti A, et al. (2016). *Self-organization of the in vitro attached human embryo*. *Nature* **533**, 251–254

<sup>25</sup> <http://www8.nationalacademies.org/onpinews/newsitem.aspx?RecordID=11282018b>

<sup>26</sup> <https://www.sciencemaq.org/news/2019/08/did-crispr-help-or-harm-first-ever-gene-edited-babies>

<sup>27</sup> <https://www.who.int/news-room/detail/26-07-2019-statement-on-governance-and-oversight-of-human-genome-editing>

## Mitochondrial replacement therapy versus germline genome modification

Mitochondrial replacement therapy is a treatment already in use which affects the next generation. The therapy involves the transfer of healthy mitochondria from a donor to replace damaged mitochondria in an unfertilised egg. Once fertilised, the embryo will have genomic DNA from the mother and father, as well as mitochondrial DNA from the donor egg. This has led some people to argue that this should be classified as germline modification. However, this therapy changes the combination of nuclear and mitochondrial DNA, rather than editing sequences. Dr Chan argued that mitochondrial replacement therapy and germline genome editing are different, that risks should be assessed independently, and that the technologies should be considered separately for regulatory purposes. In the UK, heritable genetic modification for reproductive purposes is currently not permitted by law, however mitochondrial replacement therapy is a specific exception.

## Working towards a consensus

Expert bodies are currently attempting to set out a scientific approach to assessing safety and risk for germline genome modification in a similar way to mitochondrial replacement therapy. Heritable germline editing will affect future generations, which substantially increases the risk associated with the treatment. However, while somatic genome editing is often assumed to be safer, it may not be as effective for certain conditions. Furthermore, heritable genome editing is a one-off procedure, while there is the cumulative risk of somatic genome editing procedures through generations.

There have been numerous consultations, expert reports and policy recommendations on germline genome editing. The panel highlighted the work of the International Commission on the Clinical Use of Human Germline Genome Editing, which has convened academies of science and medicine around the world.<sup>28</sup> The Commission aims to 'develop principles, criteria and standards for the clinical use of genome editing of the human germline, should it be considered to be acceptable by society'.<sup>29</sup> A consistent feature of all of these pieces of work has been public engagement. Broad public consensus is needed before moving ahead with

<sup>28</sup> <http://nationalacademies.org/gene-editing/international-commission/index.htm>

<sup>29</sup> <https://royalsociety.org/topics-policy/projects/genetic-technologies/international-commission/>

germline technologies. Engaging members of the public to help them understand these complex issues is essential to allow an informed discussion.

Participants discussed what may constitute an acceptable and responsible use of heritable genome editing during *in vitro* fertilisation and, if technically plausible, *in utero*. A better understanding of the technology and its clinical implications is required before the potential risks and benefits of such uses can be robustly analysed. The Alliance of Regenerative Medicine recently released a Therapeutic Developers' Statement of Principles, providing a bioethical framework for clinical applications of genome editing.<sup>30</sup> In this statement, it was made clear the difference between somatic and germline editing stating that germline genome editing is currently inappropriate in human clinical settings. This was signed by companies currently developing genome editing therapies, including Intellia Therapeutics.

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<sup>30</sup> <https://alliancerm.org/press-release/the-alliance-for-regenerative-medicine-releases-statement-of-principles-on-genome-editing/>

# Conclusion

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In his closing statement Professor Sir Robert Lechler PMedSci reinforced the view that human genome editing is an exciting field of medical advance with enormous potential. Genome editing is being used to tackle some of the biggest challenges in our understanding of genetic and rare diseases, paving the way for transformative medicines. In the clinic, genome editing has prospects beyond simple monogenic disorders, and we will soon begin to see these efforts realised in patients.

However, genome editing will impact both individuals and society as a whole. It is crucial that meaningful and responsible discourse with members of the public and patients on genome editing is maintained. This will require active cultivation of the science-society relationship and global governance of the science to maintain public trust. The UK regulatory system is a national strength and perceived internationally as one of the best regulatory models in the world. Due consideration should be given to the benefit and risk of these new genome editing technologies. Furthermore, the most appropriate regulatory and commercial models need to be determined to ensure the safety of, timeliness of, and accessibility to such therapies. As a leader in this area, the UK should be at the forefront of these discussions.



# Annex I - Agenda

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Thursday 5 September 2019, 14.00-17.00

Hallam Conference Centre, 44 Hallam St, Marylebone, London, W1W 6JJ

14.30-15.00	<b>Registration and refreshments</b>
15.00-15.15	<b>Welcome and introduction</b> Professor Sir Robert Lechler PMedSci, President, Academy of Medical Sciences
15.15-15.50	<b>Keynote</b> Dr John Leonard, Chief Executive Officer, Intellia Therapeutics
15.50-16.50	<b>Panel discussion: 'The Promise of Human Genome Editing for Rare and Genetic Diseases'</b> <i>Chaired by Professor Sir Robert Lechler PMedSci, President, Academy of Medical Sciences</i> <ul style="list-style-type: none"> <li>• <b>Dr John Leonard</b>, Chief Executive Officer, Intellia Therapeutics</li> <li>• <b>Dr Mathew Garnett</b>, Group Leader, Wellcome Sanger Institute</li> <li>• <b>Dr Nicola McCarthy</b>, Business Unit Manager, Horizon Discovery</li> <li>• <b>Dr Alison Kay</b>, patient representative</li> <li>• <b>Dr Sarah Chan</b>, Chancellor's Fellow, University of Edinburgh</li> </ul>
16.50-17.00	<b>Closing comments from the President of the Academy of Medical Sciences</b> Professor Sir Robert Lechler PMedSci, President, Academy of Medical Sciences
17.00-18.30	<b>Drinks reception</b>

# Annex II – Attendee list

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## Chair

**Professor Sir Robert Lechler PMedSci**, President, Academy of Medical Sciences

## Keynote speaker

**Dr John Leonard**, President and Chief Executive Officer, Intellia Therapeutics

## Panellists

**Dr Sarah Chan**, Chancellor's Fellow, University of Edinburgh

**Dr Mathew Garnett**, Group Leader, Wellcome Sanger Institute

**Dr Alison Kay**, patient representative

**Dr Nicola McCarthy**, Business Unit Manager, Horizon Discovery

## Attendees

**Dr Kate Adcock**, Director of Research and Innovation, Muscular Dystrophy UK

**Dr Janet Allen**, Director of Strategic Innovation, Cystic Fibrosis Trust

**Dr Michael Batchelor**

**Mr Steve Bates OBE**, Chief Executive Officer, BioIndustry Association

**Professor David Beeson FMedSci**, Professor in Molecular Neuroscience, NDCN University of Oxford

**Professor Shom Shanker Bhattacharya FRSE FMedSci**, Emeritus Professor of Experimental Ophthalmology, UCL Institute of Ophthalmology

**Dr Sarion Bowers**, Research Policy Advisor, Wellcome Trust Sanger Institute

**Ms Georgina Brand**

**Ms Connie Burdge**, Policy Adviser, Royal Society

**Mr Andrew Calvis**, Finance Assistant

**Dr Rosa Castro**, Senior Scientific Policy Officer, FEAM Federation of European Academies of Medicine

**Ms Victoria Charlton**, Researcher, Department of Global Health and Social Medicine, King's College London

**Dr Hayley Clissold**, Policy Officer, Wellcome Trust Sanger Institute

**Dr Elisa Corritore**, FEAM Forum Policy Officer, Federation of European Academies of Medicine

**Dr Catriona Crombie**, Philanthropic Fund Manager, LifeArc

**Dr Thomas Cunningham**, Senior Investigator Scientist, MRC Harwell

**Dr Bryan Deane**, New Medicines and Data Policy Director, Association of the British Pharmaceutical Industry

**Ms Jesmine Dhooper**, Medical student

**Ms Molly Dineen**, Masters Student, University of Exeter

**Ms Liberty Dixon**, Head of Science & Scenarios, Department of Trade

**Professor Paul Farrell FMedSci**, Professor of Tumour Virology, Imperial College London

**Dr Robin Fears**, European Academies Science Advisory Council, Biosciences Programme Director

**Dr Maria Eugenia Fernandez-Suarez**, Newton International Fellow

**Professor Elizabeth Fisher FMedSci**, Professor of Neurogenetics, University College London

**Mr Martin Gadsden**, Programme Manager, Japan Agency for Medical Research and Development

**Dr Charles Gillies O'Bryan-Tear**

**Mr Anthony Glastonbury**, Mechanical Engineer

**Professor Uta Griesenbach**, Professor of Molecular Medicine, Imperial College London

**Dr Jeremy Haigh**, Chairman, Cogent Skills

**Mrs Dina Halai**, Scientific Policy Manager, HFEA

**Dr Jennifer Harris**, Policy Executive, Association of the British Pharmaceutical Industry

**Mr Jonny Hazell**, Senior Policy Adviser, The Royal Society

**Professor Victor Hoffbrand FMedSci**, Emeritus Professor of Haematology, University College London

**Dr Harren Jhoti FRS FMedSci**, President and CEO, Astex Pharmaceuticals

**Professor Martin Johnson FRS FMedSci**, Emeritus Professor of Reproductive Sciences, University of Cambridge

**Dr Andy Jones**, Challenge Director – Medicines Manufacturing, UKRI

**Dr Jonathan Jones**, Senior Medical Director Northern Europe, Vertex Pharmaceuticals

**Dr Meghan Larin**, Research Associate

**Mrs Laurence Legros**, Executive Director, FEAM Federation of European Academies of Medicine

**Dr Louise Leong**, Director of Partnerships and Industry, Medical Research Council

**Ms Amardeep Mann**

**Dr Anji Miller**, Senior Business Manager, LifeArc

**Dr Kyriacos Mitrophanous**, Chief Scientific Officer, Oxford BioMedica

**Ms Hilary Newiss**, Chair, National Voices

**Ms Sarah Norcross**, Director, Progress Educational Trust

**Dr Stephen Oakeshott**, Head of Innovative Technologies, MRC UKRI

**Dr Martin O'Kane**, Head of Clinical Trials Unit, MHRA

**Mr Sam Parsons**, Account Executive, Hanover Communications

**Professor Jeremy Pearson FMedSci**, Associate Medical Director (Research), British Heart Foundation

**Sir Denis Pereira Gray OBE FMedSci**

**Dr Marcia Philbin**, Chief Executive, Faculty of Pharmaceutical Medicine (FPM)

**Dr Monika Preuss**, Head of Genomics Science and Emerging Technologies, UK Department of Health

**Dr Ahad Rahim**, University College London

**Professor Ulrich Rass**, Professor of Genome Stability, Sussex University

**Dr Alexander Renziehausen**, Programme Manager, NCRI

**Dr Joseph Salem**, Foundation Doctor

**Dr Victoria Salem**, Clinical Lecturer, Imperial College London

**Professor Sir Nilesh Samani FMedSci**, Professor of Cardiology, BHF Cardiovascular Research Centre

**Sir James Smith FRS FMedSci**, Director of Science at Wellcome and Visiting Group Leader at the Francis Crick Institute, Wellcome Trust

**Ms Jennifer Smoter**, Chief External Affairs & Communications Officer, Intellia Therapeutics

**Dr Jayne Spink**, Chief Executive, Genetic Alliance

**Dr Pavar Sreenivasarao**, Education & Journalism

**Mr Henry Stemplewski**, Expert Non-clinical Assessor, Medicines and Healthcare products Regulatory Agency

**Dr Ryo Takagi**, Director, Japan Agency for Medical Research and Development

**Ms Ju-Ee Tan**, Pharmacist

**Dr Susan Tansey**, Independent Consultant Pharmaceutical Physician  
**Professor Sir John Tooke FMedSci**, Professor of Medicine, Academic Health Solutions  
**Professor Richard Trembath FMedSci**, Executive Dean of the Faculty of Life Sciences and Medicine, King's College London  
**Ms Sophia Turner**, Epidemiology  
**Professor Veronica Van Heyningen CBE FRS FRSE FMedSci**, Honorary Professor and Visiting Scientist Institute of Ophthalmology, University College London  
**Ms Rosie Waldron**, Head of Public Engagement, Francis Crick Institute  
**Dr Andrew Wilfin**, Medical Director, Vertex Pharmaceuticals  
**Professor Roger Williams CBE FMedSci**, Director, Institute of Hepatology  
**Professor Robert Williamson AO FRS FMedSci**, Professor of Medical Genetics, University of Melbourne  
**Ms Cynthia Wong**, MSc Student  
**Mr Alex York**, Researcher, University of Wollongong

#### **Secretariat and staff**

**Dr Elizabeth Benedikz**, Programme Officer, Academy of Medical Sciences  
**Ms Elizabeth Bohm**, Interim Director of Medical Science Policy, Academy of Medical Sciences  
**Ms Melanie Etherton**, Communications Officer (Events), Academy of Medical Sciences  
**Dr Katarina Kolaric**, Programme Officer, Academy of Medical Sciences  
**Ms Joely Kellard**, Policy Intern, Academy of Medical Sciences  
**Ms Emma Laycock**, Policy Officer, Academy of Medical Sciences  
**Dr Tom Livermore**, Policy Manager, Academy of Medical Sciences  
**Ms Debbie Malden**, Policy Intern, Academy of Medical Sciences  
**Ms Sarah Porter**, Fundraising Manager, Academy of Medical Sciences  
**Dr Rachel Quinn**, Interim Executive Director, Academy of Medical Sciences  
**Ms Alex Straw**, Programme Officer, Academy of Medical Sciences  
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