Great Power, Greater Responsibility.

Ethical Implications on the Genome Editing Frontier

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In 1993, responding to the continually emerging and prospective possibilities of genome editing in the field of agricultural modification, social theorist Jeremy Rifkin proclaimed: "The devil is already at the door, cleverly disguised as an engineer."[1] Whilst Riskin's assessment of the genomic revolution that would erupt in the following 27 years and expand to patient therapy perhaps skewed negatively, the social theorist's concerns were by no means unfounded. In fact, Riskin's scepticism foregrounded one of the most serious ethical debates to grip the scientific community in recent memory. As technological capacity advances in the genomic field and aspirations for therapeutic application grow more optimistic, so too do important conversations need to be had regarding the proper use of such applied science. One such conversation captivated the intellectual curiosity of a London, UK, audience when The Royal Society, in partnership with Bristows, hosted an event in November of 2019 titled "The Quest for the Perfect Human..? A Debate on the Implications of Human Genome Editing." The discussion broached the increasingly apparent ethical responsibilities of the scientific community, with panellists and audience members discussing how we got to where we are, what we can do, what we can't do, and what we should do.

Dr Helen O'Neill, lecturer in reproductive and molecular genetics at University College London, London, opened proceedings with the difficult task of briefly summarising an intricate technology under scrutiny: CRISPR-Cas9. She began by acknowledging that while genetic editing attempts exist dating back 50 years, CRISPR has been used as an inherent and natural mechanism within bacteria for an estimated 3.5 billion years. In this model, CRISPR works through

the acquisition and assimilation of foreign genetic material into the bacterial genome as a means to confer immunity in the organism. To alternatively utilise this function as means to introduce sequence-specific edits in gene therapy approaches remains one of the most innovative bacterial-derived applications to date.

Realisation of the fact that this system can be exploited in such a way for genetic engineering,[2] as well as the benefits relating to its ease of use, adaptability, and affordability, led to the attention of the scientific community being assuredly piqued: "Since the acronym was coined in 2002, there are now 19 million hits on google for CRISPR," highlighted Dr O'Neill, who also noted that since 2012 there have been an estimated 5,000 related-publications and at least 2 babies born through the technology's assistance. "This is nothing short of a nucleotidal wave." Be it incorporation into immunotherapeutic regimens for cancer, to the correction of congenital defects in embryos, CRISPR appears to be growing from strength-to-strength. Despite, or perhaps because, of this increasing applicability, Dr O'Neill eluded to a range of ethical and regulatory questions that remain unanswered.

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Dr Nessa Carey was next to address the audience. A visiting Professor from Imperial College London, London, Dr Carey highlighted one of the most important distinctions to be acknowledged in the gene editing debate. Generally, this technology is referenced in application to either the soma or the germ line. In the former, localised and disease-tailored editing can be administered in an individual to ameliorate symptoms and potentially cure conditions, as seen successfully in cystic fibrosis[3] and muscular dystrophy.[4] Not unlike other pharmaceutical therapies, these treatments go through rigorous development pipelines subject to strict regulatory guidelines. However, a key difference exists in that these interventions cannot be withdrawn. Once a patient's DNA has been edited, the change is permanent notwithstanding further CRISPR utility. Such permanence emphasises the significance of DNA tampering, yet the technology is employed precisely for this kind of longstanding effect. "During almost all drug discovery, one of the major things we try to do is prevent changes to the DNA of the patient; with this technology, we're actually trying to change the DNA," reflected Dr Carey.

Often, however, it is the application of gene editing to the germ line that attracts the most controversy. Germ line editing entails the use of this technology in embryos at an early stage of development to remove deleterious alleles. This means that during the subsequent mitotic and differentiative processes each cell will inherit the edit. Far further down the developmental cascade into maturity, this also permits the possibility of the edited individual's offspring inheriting a haploid copy of the alteration. As a consequence, CRISPR has the potential to influence individual characteristics and variance on a population-wide scale. Dr Carey noted that although such technology would initially be rolled out to a very small number of cases, the ethical questions remain just as important; not only are these embryos incapable of giving consent, but the justification of the edit can be brought into question when considering the morbidity of the 'disease' being met. Take the example of congenital deafness: can we really consider this condition life limiting? Furthermore, does widespread application of gene editing to eliminate congenital deafness lead to marginalisation of present-day deaf communities, in which better-suited help could be provided through societal change? Dr Carey argued that an appreciation of medical and social models of disability is central to the genetic engineering debate.

Ethical considerations regarding gene editing are not the only concerns held by the scientific community, a message delivered by Prof Robin Lovell-Badge, senior group leader and head of the laboratory of stem cell biology and developmental genetics at the Francis Crick Institute in London, UK. The regulation of such powerful technology is highly complex, partly due to the aforementioned distinction between somatic and germ line modification, but also because of the undeniable risks associated: "I think it's generally implicit that as long as you are doing good, it's ok; the question is, are we

doing good?" Today's headlines are replete with shining stories of success related to advances made in genetic engineering. Despite these studies working well in a lab environment, however, translation to the clinic is far-away yet. The potential for undesirable effects on the target loci being modified,[5] or indeed off-target effects altogether,[6] means that currently the risks are simply too great to allow germline editing with CRISPR to be readily adopted into clinics worldwide. Yet the promise of this technology is alluring enough to consider a gentle push on the brakes as opposed to an emergency stop.

Prof Lovell-Badge informed the audience of the concentrated efforts being made by the World Health Organization (WHO) to help regulation in preparation for this future, in which a select committee has been formed to aid with this technology's governance. Considering the vast legislative, financial, and sociocultural differences between countries, a blanket set of regulatory rules for germline editing is unlikely to be effective; instead, this committee are in the process of formulating a framework to offer guidance to countries in an individualised manner. This is a complicated process, but it is encouraging to see preparatory steps being taken towards an eventuality where genome editing is globally accessible.

Offering a different perspective to the debate, Dr Rodger Novak, co-founder and president of CRISPR Therapeutics©, reflected on his involvement with genetic engineering on a commercial platform. Recognising the perceived immaturity, and indeed complexity, of this technology back in 2012, Dr Novak and his associates first highlighted the prime capabilities of CRISPR editing in an attempt to delineate a business model to pursue: genetic knock-down through non-homologous end joining,[7] insertions of exogenous DNA templates into the double helix,[8] and epigenetic regulation of gene expression using a deactivated form of the excision machinery.[9] Believing foremost in CRISPR's natural function, a focus on developing scalable knock-down strategies was chosen, all facilitated *ex vivo* to best optimise these therapies before reintroduction to the patient.

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Fast-forward to the present day, and CRISPR Therapeutics are currently involved in three active clinical trials: two investigating the haemoglobinopathies sickle cell anaemia and β-thalassaemia, and another investigating T-cell editing for allogenic therapy. Early results from the β-thalassaemia trial have already shown that a patient treated with the gene-editing machinery is now transfusion-independent:[10] a landmark achievement in haematological research. Assuming that CRISPR gene editing becomes further implemented in the clinical trials of various therapeutic disciplines, Dr Novak considered the need for new economic models that place patient outcomes at the centre of the pricing decision-making process. This model of pricing will undoubtedly bring its own challenges: the true 'success' of genome-editing therapy would need to be determined over an extensive time period, and the emergence of unexpected side-effects at later dates may also complicate matters. Much like the individuality of the therapy itself, however, pricing must surely adopt a patient-centric consideration.

As the debate was opened up to the audience in attendance, further vital arguments were brought to light. Following one question, in which a member of the audience asked how the public can develop trust in the regulatory bodies towards the proper use of such powerful technology, Prof Lovell-Badge emphasised the importance of appropriate public engagement from the earliest stages of regulation. He spoke of the concerns that members of the scientific and wider communities had regarding the lax regulatory approach of certain countries, referencing 'rogue' stem cell clinics that have arisen which are offering therapies to patients in desperate need of help. Such unregulated practice is often dangerous and lacking in actual clinical benefit, with the prospect of similar conduct with gene editing not a comfortable one. To this effect, the dissemination of accurate information to societies across the globe is of the utmost importance. Dr Novak concurred, speaking of the need to communicate with these countries in which disreputable practice is rife as well as to those who are, arguably, introducing CRISPR too readily into the clinic.

One audience member raised the possibility of using germline editing to completely eliminate genetic disease in three generations' time, and what this reality could look like. The speakers were unanimous in agreeing that this is likely impossible; Dr Carey pointed out that although this could feasibly be achieved temporally in one family, the occurrence of *de novo* disease-causing mutations in individuals, along with the fact that many diseases manifest through the homozygous coupling of recessive mutations over generations, means that genetic diseases are somewhat inevitable in their appearance in the population. Dr O'Neill agreed with this sentiment, adding that the reality of *de novo* mutagenesis means that despite the fact preimplantation genetic screening and diagnosis have been used in clinics for some 30 years, genetic disease is nowhere close to being eliminated.

Another impassioned attendee decried the lack of apparent objection to the use of genome editing during the debate, particularly in regard to germline alteration. Highlighting the current climate of social inequality and authoritarianism, they expressed deep concerns of CRISPR misuse to further eugenics movements. Dr Carey countered this point with referral to a case report she had discussed with her students involving a family tree afflicted with Huntington's disease. The hopeful mother who carried the deleterious allele carried out preimplantation genetic screening of the limited amount of eggs she could produce to find a disease-free candidate. A concession of 10 embryos were terminated, an emotionally devastating ordeal for the family that Dr Carey argued had the potential to have been prevented with CRISPR: "We need to flip the question from what right do we have to intervene, to what right do we have to withhold this from a family who are really desperate for it?" Both Dr Novak and Prof Lovell-Badge agreed in emphasising the potential application of this technology in patient or family-centric scenarios, purely for the prevention of disease burden as opposed to characteristic correction.

A resonant question to conclude the debate came from another member of the audience in referral to the title of the event: what does the perfect human look like? Dr O'Neill was steadfast in her dismissal of such an entity, proclaiming that we are erroneous in our making and being; even if the technology was to be perfected to the point of no off-target effects or risk, scientists would still be working with the most flawed biological model in human reproduction and biology. Dr Carey took this sentiment further, stating: "The idea of a perfect human is biologically irreverent and ethically disastrous." Indeed, this perception of perfection often lies in the eyes of the beholder, which, in the instance of implementing powerful technology, can be corrupted by the dominant socioeconomic bias. Perhaps, however, this line of thinking will, in time, become obsolete. Arguably, a re-emphasis of the intended therapeutic application of genome editing to the general public is sorely needed, especially in a time when over-sensationalised fears of 'designer babies' complicate efforts being made to meet the existing hurdles of regulatory implementation and ethical acceptance. At least for this night, these burning issues were put to rest to allow reflection on the inspired points made, but a debate of this magnitude will most certainly continue to rage for years to come.

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