Ethics in Action

Germline editing – science is outpacing the debate

Almost exactly a year after researchers at China's Sun Yat-sen University published the first-ever study on gene editing of human embryos (germline editing),[1] another Chinese research team at Guangzhou Medical University released results of its own study using CRISPR/Cas9 gene editing technology in human embryos with the aim of introducing a genetic mutation that makes humans HIV-resistant.[2]

While the global reaction to the release of the first paper bordered on explosive – spurring a comprehensive international debate as well as an explicit ban in the US on Food and Drug Administration reviews of clinical research in this area[3] – the second paper was greeted with much less dismay.

That's not to say the debate over the ethics surrounding germline editing, which could introduce genetic changes in humans that are passed down to future generations, has died down. Perhaps, however, it has evolved.

That both Chinese research groups emphasised their goals were basic research, and both used non-viable embryos, is testimony to this. So is the fact that the second paper went to some length to address ethical considerations. It poses questions such as, "How do we define the norm of human and human genome?" and "Once we understand the underlying biology, would it be acceptable to introduce alleles that improve human health and life span or to eliminate those imposing serious disease risks (eg, Huntington's disease)?"

It concludes, in part, that "because human *in vitro* fertilisation methods are well established and site-specific nuclease technologies are readily available, it is foreseeable that a genetically modified human could be generated. We believe that any attempt to generate genetically modified humans through the modification of early embryos needs to be strictly prohibited until we can resolve both ethical and scientific issues."

Moreover, in Europe two other human germline editing studies using viable human embryos have since been approved, at the UK's Francis Crick Institute and at Sweden's Karolinska Institutet.

In addition, the US National Academy of Sciences and National Academy of Medicine (NAS/NAM) are looking into the issue. They launched an initiative last year which included an international summit on human gene editing in December 2015 and several meetings organised by a committee that is carrying out a consensus study on various aspects of human gene editing technologies (including germline editing), such as its possible uses and the clinical, ethical, legal and social implications.

A NAS/NAM spokesperson has confirmed that a report on the study is expected out in early 2017. "It will aim to provide a framework based on fundamental, underlying principles that may be adapted by any nation that is considering the development of guidelines," she told *MedNous*.

Based on the conclusions at the NAS/NAM meetings to date, in which the potential benefits of human germline editing in basic research (ie, not for clinical applications) have been cautiously recognised, one might speculate with some confidence that the final report will not recommend prohibiting the activity but rather make sure it is carried out in a responsible manner. Indeed, stakeholders are treading carefully even when considering basic germline editing research.

The Nuffield Council on Bioethics in the UK published a report[4] in September 2016 which states: "A distinctive consideration relating to genome editing is that it potentially brings 'basic' biological research and translation to clinical treatment into closer conjunction. This is so because, in some cases, alteration of a genome sequence could, in principle, serve both to discover the function of the gene and to enable treatment." In other words, the proof of concept of the research technique may equally constitute a proof of concept for a prospective treatment.

Germline editing for basic research

Nevertheless, there appears to be greater acceptance, at least in the scientific community, that germline editing for basic research purposes will continue along its trajectory. This may allow scientists to refine the technology and sort out glitches such as genetic mosaicism and the introduction of off-target mutations, in turn narrowing the gap between research and innovation.

A joint policy statement released by the Wellcome Trust, the Academy of Medical Sciences, the Association of Medical Research Charities, the Medical Research Council and other UK organisations, states that research using genome editing tools "holds the potential to significantly progress our understanding of many key processes in biology, health and disease and for this reason we believe that responsibly conducted research of this type, which is scientifically and ethically rigorous and in line with current legal and regulatory frameworks, should be allowed to proceed."[5] They support the use of genome editing in preclinical biomedical research as well as studies that progress and refine these technologies, clarifying that such research may involve the use of somatic (non-reproductive) or germ cells, including human embryos up to 14 days old.

This type of general accord, as well as the absence of a dedicated legal or regulatory framework in many countries, has created a sense of urgency to obtain the "broad societal consensus" called for by the NAS/NAM, the Council of Europe Bioethics Committee and other global stakeholders, before clinical application of germline editing outpaces ethical deliberations.

"It's essential that we start these discussions early, by engaging in an open and inclusive debate involving scientists, ethicists, doctors, regulators, patients and their families, and the wider public," noted Sam Alvis, a policy officer at Wellcome, which is a sponsor of the NAS/NAM initiative. "Wellcome believes that the public debate on gene

editing more generally should be inclusive, and conducive to understanding of the technology," he added.

However, Marcy Darnovsky, executive director of the California-based Center for Genetics and Society (CGS), told *MedNous* that getting agreement from a wide range of people "is a great aspiration, but we haven't seen the national academies or anyone else taking that on in any serious way." As a speaker at the December NAS/NAM summit, she noticed that the representation from stakeholders outside the scientific community was sparse.

"As far as I could tell, I was the only public interest advocate invited. There were a few social scientists, but it's so inadequate considering what's at stake," she said, noting that the discussions were mainly technical and largely about how to make gene editing safe.

"I think a lot of the scientists just don't know what to make of the social, policy and ethical issues that are raised. It's a different way of looking at the world and I think it's another indication of how urgent it is to involve a whole lot more perspectives and voices in these discussions," added Dr Darnovsky.

People with disabilities

One voice that was notably absent from the table at the summit but that is "absolutely necessary" in the talks is the disabled community. A handful of representatives from disability rights organisations did have an opportunity to speak at a panel discussion during a February 2016 consensus study meeting in Washington, DC, but the impact on this group is far-reaching and needs to be addressed further.

For example, a future with germline editing means that society could effectively be forced to decide which genetic diseases should be engineered out of the gene pool and which should remain. The concept has been likened to modern-day eugenics.[6] Moving on from that, if gene editing is eventually allowed into fertility clinics, Dr Darnovsky said, "I don't think it's fanciful to think that researchers and fertility clinics will offer genetic enhancements."

Another related concern about using germline editing technologies to one day eradicate certain diseases is the implication that people with disabilities are living a tragic existence, with this technology being the only way to spare suffering in future generations. Similar to past arguments for commercialising preimplantation genetic diagnosis and stem cell therapy, this creates a sense of urgency for the technology to reach the clinic, potentially bypassing any well-considered ethical consideration that includes the disabled community and the public.

The CGS does not have a policy position that aims to prohibit gene editing on human embryos for research purposes, "but we're very uneasy in the absence of a legal prohibition against germline editing in reproduction," said Dr Darnovsky. "We and many others think the US should join all those dozens of countries that have clear prohibitions against using any kind of genetic modification for human reproduction."

Although the legal situation on human germline editing in Europe varies from country to country, Article 13 of the 1997 Oviedo Convention created a minimum common standard by prohibiting "modifications in the genome of any descendants."[7] It is binding law in the member states that have ratified it.

It is interesting to note that while the debate about human germline editing continues to unfold, a US fertility doctor, John Zhang, announced that he had produced the world's first 'three-parent baby' by using a controversial mitochondrial transfer technique (also known as mitochondrial manipulation).[8] According to Dr Darnovsky, the procedure is different from gene editing, but is technically a form of germline modification, which Dr Zhang acknowledged that he carried out in Mexico to evade US regulations. (The UK is the only country that has a law in place to allow mitochondrial transfer; Mexico does not have any regulations in this regard.)

The mother, from Jordan, had a mitochondrial DNA mutation known to cause Leigh syndrome, leading her to miscarry four times and lose two children. The technique Dr Zhang used involved placing the spindle of the egg, which contained the mother's chromosomes, into a donor egg from which the nuclear genetic material had been removed. Five eggs were then fertilised, resulting in one "chromosomally normal" embryo, which was transferred into the woman and resulted in the birth of an apparently healthy baby boy.

As *MedNous* went to press, Dr Zhang was due to present the case study at the Scientific Congress of the American Society for Reproductive Medicine (ASRM).

References:

1. Liang P et al, CRISPR/Cas9-mediated gene editing in human tripronuclear zygotes, *Protein & Cell*, May 2015, http://bit.ly/1EedsFn.

2. Kang X et al, Introducing precise genetic modifications into human 3PN embryos by CRISPR/Cas-mediated genome editing, *Journal of Assisted Reproduction and Genetics*, May 2016, http://bit.ly/1Nhlxuo.

3. Consolidated Appropriations Act, 2016 (Public Law 114-113), 18 December 2015, www.congress.gov.

4. Nuffield Council on Bioethics, Genome editing: an ethical review, September 2016, http://nuffieldbioethics.org.

5. Wellcome Trust et al, Genome editing in human cells initial joint statement, September 2015, https://wellcome.ac.uk.

6. Beitiks, E, 5 Reasons Why We Need People with Disabilities in the CRISPR Debates, *Biopolitical Times*, 8 September 2016, www.biopoliticaltimes.org.

7. Convention for the protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine (Oviedo Convention), 4 April 1997, www.coe.int.

8. Zhang J et al, First live birth using human oocytes reconstituted by spindle nuclear transfer for mitochondrial DNA mutation causing Leigh syndrome, ASRM, 19 October 2016, www.asrm.org.

This article was researched and written by Karen Finn, a contributing editor to *MedNous*.