PERSPECTIVE

Encourage the innovators

Rather than emphasize risks that are not entirely new, talks about germline editing should focus more on the benefits, argues **George Church**.

International scientific academies will be discussing the issue of human-germline editing in Washington DC on 1–3 December. Now is, therefore, a good time to encourage the general public to become well informed on key issues, which may get muddled by out-of-date facts or loose phrasing. This technology is poised to transform preventive medicine. Rather than talk about the possibility of banning alteration of the human germ line, we should instead be discussing how to stimulate ways to improve its safety and efficacy. I hope to rectify some common misconceptions.

The potential to alter the human germ line did not arise with the discovery of CRISPR–Cas9, nor with other genome-editing technologies such as zinc-finger nucleases (ZFNs) and transcription activator-like effector nucleases (TALENs). Gene therapy was first developed in the 1970s. And even though the term CRISPR–Cas9 has been used interchangably with gene therapy, none of the current 2,200 gene-therapy clinical trials involve this technology — but they do modify the genomes of adults and children. There is no technical reason why gene therapy could not be deployed to alter the human germ line — yet almost 80% of countries, including the United States and China, have not banned such modification[1]. In fact, germline editing can be a by-product of the systemic application of gene therapy to non-reproductive cells. A similarly little-recognized point is that the DNA of embryonic cells can be edited without affecting the germ line.

Human-germline editing is not special with respect to permanence or consent. Replacing deleterious versions of genes with common ones is unlikely to lead to unforeseen effects and is probably reversible. Even if the editing was difficult to reverse, this would not be especially unsafe compared with other commonly inherited risks. Offspring do not consent to their parents' intentional exposure to mutagenic sources that alter the germ line, including chemotherapy, high altitude and alcohol — nor to decisions that reduce the prospects for future generations, such as misdirected economic investment and environmental mismanagement.

We already know that germline editing is unlikely to cause dangerous, unforeseen mutations. In the best case scenario so far, CRISPR–Cas9 seems capable of less than 1 error per 300 trillion base pairs[2], and techniques to reduce these off-target effects using 'CRISPR pairs' might cut this by many factors of ten. That said, the issue is not simply about the number of off-target effects that might occur anywhere in the genome, but whether they appear in certain genes that, if altered, increase the risk of cancer in a particular tissue type. Given that there are about 1,200 of these tumour suppressor genes in the human genome, with a target size of about 3,000 base pairs each, the risk of an unintentional edit in one of them is a million times lower than for the genome as a whole. Using one altered germ cell rather than a billion somatic cells is very likely to be a billion times less risky because each of the billion cells has an independent chance to add to the risk of initiating cancer.

Meanwhile, human-germline editing is needed because alternative methods for preventing the transmission of inherited diseases are problematic. Prenatal genetic diagnosis during *in vitro* fertilization (IVF) is often put forward as an alternative to editing. But this does not offer a solution for someone who has two copies of a deleterious, dominant version of a gene nor for potential parents who both have two copies of a harmful, recessive version of a gene. This is a bigger problem than the population frequencies of such genes suggest — marriage between blood relations is a deeply rooted social trend among one-fifth of the world's population[3].

Those who want to ban human-germline editing should also consider that such a move would do little to allay concerns about ethically dubious attempts to 'enhance' humans. To think that there is not already a cadre of IVF clinicians poised to engage in such practices, perhaps even supported by governments, is to ignore, for example, the history of doping in sport. These kinds of ambitious individuals and institutions are unlikely to be dissuaded by an agreement made on their behalf by others with a different view.

BANNING HUMAN GERMLINE EDITING COULD PUT A DAMPER ON THE BEST MEDICAL RESEARCH, DRIVING THE PRACTICE UNDERGROUND.

Finally, the concept of a ban on germline editing does not make sense. There is already a ban on using medical technologies in humans until they are proven safe and effective in appropriate animal trials. Then, following human trials, they can only be applied to the general population for those conditions for which their use has been demonstrated. Banning human-germline editing could put a damper on the best medical research and instead drive the practice underground to black markets and uncontrolled medical tourism, which are fraught with much greater risk and misapplication. Instead, the generally high safety and efficacy standards of regulatory agencies should be encouraged rather than saddled with pessimistic assumptions about the trajectory of promising approaches.

The genome-editing community can effectively encourage researchers to pursue innovative technologies and to improve the safety and efficacy of the new tools. And, as discussion of germline editing becomes more mainstream, we should learn how to better address the concerns of those who are unfamiliar with the techniques so that the benefits, as well as the risks, are clear to them. ■

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