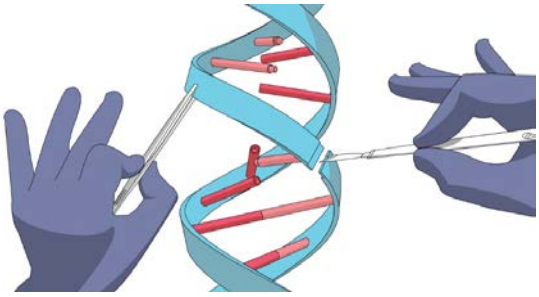
What if gene editing became routine practice?

Gene-editing techniques are still relatively new, but are constantly multiplying, and they seem exciting in their promise, especially since a more precise version – CRISPR-Cas9 – has recently been used for the first time in a human trial. The use of CRISPR-Cas9 has generated a series of socio-ethical concerns about gene editing, which trigger societal debates and regulatory initiatives.



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The announcement, in November 2016, that gene editing had been tested in a person for the first time was received as a potential 'biomedical Sputnik' moment marking a breakthrough in the field of cancer research. In February 2016, the UK became the first country to authorise the genetic modification of human embryos using CRISPR-Cas9[1] and related techniques, for research. Gene editing is a rapidly developing area of biotechnology that allows scientists to edit the genome of a living organism by inserting, deleting or replacing pieces of DNA. The capacity to engineer genomes in a systematic and cost-effective way has been a long-standing objective in the field of genomic studies.

Several gene-editing techniques have recently been developed to improve gene-targeting methods, including CRISPR-Cas9, transcription activator-like effector nucleases (TALENs) and zinc-finger nucleases (ZFNs). This multitude of techniques illustrates the potential of gene editing in targeting genes in a precise and cost-effective manner and modifying human genomes even at the embryonic stage. CRISPR-Cas9 is a powerful tool that has the potential to cut the DNA of any genome at any desired location, replace or add parts to the DNA sequence by introducing the Cas9 protein and appropriately guide RNA into a cell. It currently stands out as the biggest 'game changer' in the field of gene editing due to its efficiency and low cost. This technological trajectory is expected to enhance our capacity to target and study particular DNA sequences in the vast expanse of a genome.

Potential impacts and developments

CRISPR-Cas9, being a fast-moving technology, has a lot of potential as a tool for directly modifying or correcting the fundamental disease-associated variations in the genome and for developing tissue-based treatments for cancer and other diseases by disrupting endogenous disease-causing genes, correcting disease-causing mutations or inserting new genes with protective functions. Two first-in-human safety trials have been initiated to study whether CRISPR-edited immune cells could kill tumour cells in people with terminal cancer. Researchers hope to use it to adjust human genes to eliminate diseases, fight with constantly evolving microbes that could harm crops, wipe out pathogens and even edit the genes of human embryos, which could eventually lead to transformative changes in human well-being. CRISPR-Cas9 can be used to alter the genes of a wide range of organisms with relative precision, and also create animal models for fundamental research. Editing the genes of animals could improve disease resistance, control mosquito populations to mitigate or tackle malaria transmission, or even lead to the creation of farmaceuticals, which are drugs created using domesticated animals or crops. Recently, scientists discovered how mosquitoes become virulent virus hosts unlocking the mechanisms by which yellow fever virus (YFV), Zika virus (ZIKV)

[1] The term CRISPR/Cas9 stands for Clustered Regularly Interspaced Short Palindromic Repeats/CRISPR associated protein 9. CRISPR refers to unusual DNA sequences that can be used to protect organisms by identifying threats – especially viruses – and attacking them. The Cas9 protein is responsible for locating and cleaving target DNA, both in natural and in artificial CRISPR/Cas systems.

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and West Nile virus (WNV) antagonise antiviral small RNA pathways in disease vectors. In addition, the technique is expected to facilitate transplanting animal organs into people by eliminating copies of any retrovirus present in animal genomes that may harm human recipients. CRISPR-Cas9 may develop the potential to enable the creation of human organs in chimeric pigs, with the possibility of having an unlimited supply of organs not rejected by the immune system of human recipients.

At the same time, the use of CRISPR has generated a series of socio-ethical concerns over whether and how gene editing may be used to make heritable changes to the human genome, lead to designer babies, or even disrupt entire ecosystems, leading some scientists to recommend a moratorium on making inheritable changes to the human genome. For instance, the application of CRISPR as a pest-control technique may produce off-target effects and mutations, which could lead to the dispersion of gene drive, the disappearance of a whole animal population, or accidental releases and/or the irreversible disturbance of entire ecosystems. Taking into account the non-maleficence principle in risk assessment, and distinguishing the clinical and therapeutic aims of gene editing from its enhancement applications/uses have also become sources of major concern. Other important problems are linked to the efficient and safe delivery of CRISPR-Cas9 into cell types or tissues that are hard to transfect and/or infect. These range from the prospect of irreversible harms to the health of future children and generations, all the way to concerns about opening the door to new forms of social inequality, discrimination and eugenics. In October 2017, the Parliamentary Assembly of the Council of Europe reaffirmed its opposition to contemplating germline changes, as expressed in the 'Oviedo Convention', on the grounds that they cross 'a line viewed as ethically inviolable' (see Recommendation 2115 (2017) on the use of new genetic technologies in human beings).

Anticipatory policy-making

Given the rapid pace of scientific developments in the field of gene editing, its regulatory oversight seems more necessary than ever before. However, there is a lack of scientific and legal consensus as to whether this transformative technology should be regulated as such, or whether its techniques and products should instead be controlled individually following a result-based approach. International discussion, especially in the frame of the Nagoya Protocol, is currently focused on the regulatory status of genome-editing techniques. Within this frame, the European Commission is working on a legal interpretation of the regulatory status of products generated by new plant-breeding techniques so as to minimise legal uncertainties in this area. In July 2018, the European Court of Justice (ECJ) ruled that genome-edited organisms qualify as products of genetic engineering and hence fall under the scope of the 2001/18 Deliberate Release Directive. The Court declared that genetic modification includes genetic changes 'in a way that does not occur naturally'. The ruling emphasises that organisms obtained by mutagenesis, a set of techniques which make it possible to alter the genome of a living species without the insertion of foreign DNA, are GMOs and are, in principle, subject to the obligations laid down by the relevant EU-wide authorisation rules. Patenting CRISPR-Cas9 for therapeutic use in humans is also legally controversial. In September 2018, the US Court of Appeals for the Federal Circuit awarded, for the first time, intellectual property on the use of CRISPR in 'eukaryotic cells', which include plant and animal cells, to the Broad Institute, MIT, and Harvard, which had been the first to obtain a CRISPR patent in 2014. The risks of heritable, unintended and unpredictable genetic mutations also raise questions about the safety of the technique and the attribution of liability in case of damages. In a recent report under the title 'Gene Drives on the Horizon: Advancing Science, Navigating Uncertainty, and Aligning Research with Public Values', the US National Academies of Sciences, Engineering, and Medicine urged caution when releasing gene drives into the open environment and suggested 'phased testing', including special safeguards in view of the high scientific uncertainties and potential ecological risks.

In fact, many scientists caution that there is much to do before CRISPR is deployed in a safe and efficient manner, given that anyone with the appropriate equipment could engineer a vaccine-resistant flu virus or invasive species in a laboratory. Finally, yet importantly, CRISPR might create additional challenges from a risk assessment standpoint, in that organisms produced by these methods may contain more pervasive changes to the genomes of living organisms than traditional genetic modification techniques. Given the variety of concerns surrounding the potential unintended consequences of these techniques, public debates on responsible use of this promising technology are needed at local, national and supranational levels.