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Governance of gene editing in South Africa: Towards addressing the ethico-legal hiatus

Advances in biotechnology have made human gene editing a reality. Progress in the field is gaining momentum and promises for well-being at a level not previously imagined emerge. This progress also raises ethical, legal and social considerations together with valid concerns that the law and ethics are lagging behind. Gene editing involves precise additions, deletions and alterations to the genome. Basic science research in gene editing is already underway in laboratories globally. Clinical applications involving somatic (non-reproductive) cells are in the early stages and, going forward, there is great potential for the use of this technology in germline cells. Currently, South Africa does not have an ethico-legal framework in place for the governance of gene editing, and while we contemplate catching up in this regard, the first CRISPR-edited babies have already arrived.[1] The First South African Conference on Gene Editing – an initiative of the South African Medical Research Council (SAMRC) and the Faculty of Health Sciences of the University of the Witwatersrand – brought together local and international experts at the end of November 2019 to discuss and debate these issues and to inform appropriate and relevant recommendations. The conference organisers were Professors Glenda Gray, Ames Dhai, Martin Veller and Daynia Ballot.

Gene editing: The global situation

Seven years ago, researchers discovered that CRISPR-Cas9, a molecular defence system used by microbes to resist viruses and other invaders, could be utilised to edit human genes. Following this discovery, CRISPR's ability to disable or correct problematic genes in cells as a therapeutic modality for a number of diseases was, and continues to be, researched. Treating diseases with the use of the genome-editing tool CRISPR is rapidly becoming a reality with applications to medical uses of CRISPR-Cas9 gaining momentum in 2019. Several trials were launched and the results from some of the first trials were available during the course of the year. More than a dozen active therapeutic studies testing the ability of CRISPR-Cas9 to treat a range of diseases from cancer to HIV and blood disorders had been listed on the US government's clinicaltrials.gov database in 2019. However, robust conclusions on the safety and efficacy of CRISPR-Cas9 therapies cannot yet be drawn, because thus far only a few people have been treated in these trials. Despite the promising CRISPR gene-editing results, it is premature to make conclusions as to whether the technique will be as safe or effective as medical therapy. In addition, some gene-editing tools like prime editors that were first reported late last year, while holding the promise of being more precise and controllable than CRISPR-Cas9, are currently too large to fit inside commonly used gene-therapy viruses. Nevertheless, scientists and researchers are confident that in the future there will be more sophisticated applications of CRISPR gene editing that could underpin the treatment of a host of diseases. The benefits include gains in public health with gene editing assisting in eradicating diseases of poverty, including those that are infectious.[2]

Gene editing for medical therapeutic applications using somatic cells, while scientifically complex, is not controversial. Genetic changes made to somatic cells in gene therapy is an established modality of treatment and gene editing for somatic applications would not be dissimilar.[3,4] However, gene editing has the potential to modify embryos (germline gene editing), raising ethical, legal, and social complexities, in particular when those embryos are allowed to fully develop to parturition. The importance of gene-editing research of germline cells is that the understanding of human development and fertility will be enhanced, allowing for progress in fertility treatments, regenerative therapies, and other related medical applications. Prevention of disease transmission is currently possible with the use of prenatal and preimplantation genetic diagnosis. The problem, however, is that these technologies do not work in some cases, and where they do work, this could result in discarding affected embryos, or in selective abortion, giving rise to 'beginning of life' debates. Some families could be provided with the most suitable option for averting disease transmission with germline gene editing and the resulting genetic changes would then be passed down the generations. It is this shift from individual level effects and, in particular, the responsibility to future generations that some people consider contentious. Social and ethical concerns also include the acceptance of children with disabilities, the risk of inheriting off-target genome effects, equitable access, and enhancement with slippery slope arguments in the context of eugenics. Enriching traits and capacities beyond levels considered adequate for health are realistic possibilities. Considerations involving fairness, social norms, and the need for both public debate and regulations hence arise.[3-5]

Other concerns hinge on biosecurity and the potential of gene editing for dual use research where gene-edited bioweapons or out-of-control gene drives could be produced. Fears have also been raised over unforeseen ecological impacts. In addition, gene drives could be weaponised to wipe out agricultural systems or to spread a deadly disease. The US Defense Advanced Research Projects Agency (DARPA) believes that adverse events in clinical trials or the nefarious use of genome editors may only be recognised well after these occur and therefore CRISPR must be contained. DARPA, in 2017, launched the Safe Genes programme, a 4-year initiative with the purpose of combating the dangers of CRISPR technologies.[6]

In 2017, the US National Academy of Sciences, pursuant to broad consultation, recommended that heritable genome editing clinical trials be permitted within a framework of due care and responsible science and stipulated that the following criteria be satisfied[5]:

- *absence of reasonable alternatives;*
- *restriction to preventing a serious disease or condition;*
- *restriction to editing genes that have been convincingly demonstrated to cause, or to strongly predispose to, the disease or condition;*

- *restriction to converting such genes to versions that are prevalent in the population and are known to be associated with ordinary health with little or no evidence of adverse effects;*
- *availability of credible preclinical and/or clinical data on risks and potential health benefits of the procedures;*
- *ongoing, rigorous oversight during clinical trials of the effects of the procedure on the health and safety of the research participants;*
- *comprehensive plans for long-term, multigenerational follow-up that still respect personal autonomy;*
- *maximum transparency consistent with patient privacy;*
- *continued reassessment of both health and societal benefits and risks, with broad ongoing participation and input by the public; and*
- *reliable oversight mechanisms to prevent extension to uses other than preventing a serious disease or condition.*

The US Academy further proposed seven principles for the governance of human genome editing: promoting well-being, transparency, due care, responsible science, respect for persons, fairness and transnational cooperation.[5]

In 2018, the UK's Nuffield Council of Bioethics proposed two principles on the ethical acceptability of genome editing in the context of reproduction that must be met[7]:

- Firstly, the intention of the intervention should be to secure the welfare of the individual born as a result of such technology. In addition, the intervention must be consistent with the welfare of such a person.
- Secondly, principles of social justice and solidarity must be upheld, and the intervention should not result in an intensifying of social divides or marginalising disadvantaged groups in society.

In November 2018, the US Academy, in collaboration with the Hong Kong Academy of Sciences, convened a major international meeting on gene editing with a key goal being to reach international consensus on how germline editing should proceed. Many scientists and ethicists had been pushing for the creation of ethical guidelines as they believed it was inevitable that genome-editing tools would be used by some to make changes to human embryos for implantation into women. Just prior to the summit, He Jiankui, a Chinese biophysicist, announced that he had created the world's first gene-edited babies.[8]

He Jiankui created a global outcry when he announced that his team at Southern University of Science and Technology in Shenzhen had made and implanted human embryos less susceptible to HIV by editing their DNA with the use of the CRISPR gene-editing system. His actions were condemned because gene-editing technology was regarded as too premature to be used for reproductive purposes and there was a risk of introducing mutations with potentially harmful effects. In addition, because the babies were not at high risk of contracting HIV, the gene editing conferred little benefit. There were speculations and concerns that other scientists would follow in his footsteps.[8] He was fired from his University in January 2019. The following December a Chinese court sentenced him to 3 years in prison for illegal medical practice and a fine of 3 million yuan (USD430 000). Shorter sentences and fines were handed down to two colleagues who assisted him. They too have been banned from working with human reproductive technology ever again by the health ministry and from applying for research funding from the science ministry. Chinese scientists believe that the punishments are likely to deter others from similar conduct.[9]

Hot on He Jiankui's heels, Denis Rebrikov, a Russian scientist, announced his plans to produce HIV-resistant babies in June last year.[10] Once again, there was an outcry from international researchers who claimed that the benefits, i.e. possible resistance to HIV, were not worth the unknown risks of gene editing, and that there were other ways to prevent mother-to-child transmission of the virus. The Ministry of Health of the Russian Federation subsequently released a statement stating that the production of gene-edited babies was premature, halting Rebrikov's plans to implant the embryos.[11]

Soon after He's announcement in November 2018, the World Health Organization (WHO) established a committee of global experts to develop an international framework for the governance of the clinical use of gene editing. In August 2019, this WHO committee launched an international registry of clinical research that used gene editing in humans in order to oversee this practice. The US National Academy of Sciences, the US National Academy of Medicine and the Royal Society of the United Kingdom also established an international commission to prepare a framework to guide clinical research in germline gene editing. This framework is expected to be released towards the middle of 2020.[11]

Many researchers have reacted by calling for a moratorium on gene editing in embryos and germline cells.[12] However, recent surveys suggest that the public supports genome editing in embryos for the treatment of disease-causing mutations. A survey conducted by the Nuffield Council of Bioethics in the UK in December 2017 showed that almost 70% of the 319 participants supported germline gene editing for the treatment of infertility, or for altering a disease-causing mutation in an embryo.[13] A larger survey involving 4196 Chinese citizens reported a similar level of support for germline gene editing with the aim only of avoiding disease. These respondents were opposed to using it to enhance IQ or athletic ability, or to change skin colour.[8]

Outcomes of the First South African Gene Editing Conference

There was general agreement at the First South African Gene Editing Conference[14] that Africa is ready for somatic gene editing, and that this technology has a major role to play in addressing the African disease burden. The role of gene editing in inherited bleeding disorders, and in the context of a cure for chronic hepatitis B virus infection, was highlighted. Arguments based on scientific and human equality were used to stress that Africa is definitely a home for human gene editing. All humans, including Africans, have equal dignity and potentially possess equal capabilities, despite having unequal capacity, opportunities and incentives. If Africa is deprived of gene editing research, this could result in creating further health inequalities and perpetuate the 10–90 gap. Scientific equity should be considered as the means and process of achieving equality.

The following values, norms and standards were emphasised repeatedly by delegates and presenters at the conference:

- There is a need for transparency in scientific and governance processes.
- Vigorous communication is required at several levels including with the public.
- The justice principle must be foremost, in that there ought to be equitable access to these technologies.
- Gene editing should not be allowed to result in increasing our current disparities.
- Patient centricity, autonomy, the public and common good are essential considerations.
- Safety is paramount with protections extending to future generations.
- Research must be conducted responsibly with integrity being pivotal.

There was agreement that a robust and enforceable ethico-regulatory framework for gene editing, which includes these norms and standards, is needed as a matter of urgency. To this end, there was an undertaking by Professor Glenda Gray, President of the SAMRC, to establish a Working Group comprising multidisciplinary experts and representatives from relevant government departments to develop a national framework for the governance of gene editing.

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