Can human germline alterations be ethically justified?

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It is well known that every scientific and technological development is ambivalent in the sense that it can contribute to improving people's quality of life but, at the same time, may bring new harms to individuals, society and the environment. Moreover, with the increasingly accelerated pace of science, this ambivalence becomes even more dramatic, since every new technology can be used for better or for worse.

Life sciences illustrate very well this challenging ambiguity of technology. As Michael Selgelid points out, life scientists today are in a situation similar to that of atomic physicists in the early 20th century, whose key discoveries enabled the production (and use) of the first atomic bombs in Hiroshima and Nagasaki [1]. Like nuclear technology, formidable developments in the life sciences, especially in genetics, may bring great benefits to humankind, but could also have catastrophic consequences if used irresponsibly.

A recent example of this ambivalence is the genome-editing method called CRISPR-Cas9. This technique, developed in 2012, allows scientists to easily eliminate or replace sections of DNA with greater precision and at much lower cost than previous methods. The possibility of cutting and pasting genes with astonishing ease opens up extraordinary opportunities for applications in the agricultural and livestock sectors, in biotechnology and in biomedicine. It is therefore not surprising that over the past few years uncounted laboratories around the world have begun to use CRISPR-Cas9 in very different research areas.

In the biomedical field, genome editing on somatic cells holds great therapeutic promise for the treatment of HIV/AIDS, leukemia, thalassemia, cystic fibrosis, hepatitis B, Duchenne muscular dystrophy, Huntington's disease, cancer and many other severe diseases [2, 3]. In addition, genome editing in non-human animals could contribute to the prevention and treatment of various medical conditions. For instance, the prospect of xenotransplantation is currently enjoying a revival as the gene editing of pig organs might reduce the risk of rejection and transmission of infections to humans [4]. Genome editing could also help fight malaria by genetically modifying the population of mosquitoes that act as vectors for the disease [5].

When we consider genome editing in humans through ethical and legal lenses, a crucial distinction is usually made between the alteration of *somatic* cells (i.e. body cells) and *germline* cells (i.e. oocyte, sperm, and early embryos). Given that gene editing of *somatic* cells only affects the individual treated by the intervention, it does not in principle raise ethical questions other than those related to the risks inherent in any new, experimental therapy. By contrast, alterations in the human *germline* pose unprecedented concerns, given that the altered genes will be passed on to future generations, potentially causing them irreversible damage and raising the specter of 'designer babies', whereby embryos are genetically modified to enhance them according to the parents' wishes [6, 7].

Precisely in response to the concerns for the integrity of future generations, a global consensus emerged in the 1990s about the need to ban genetic engineering of the human germline. In 1997, representatives of 186 states, meeting at the UNESCO headquarters in Paris, unanimously approved the *Universal Declaration of the Human Genome and Human Rights*. This document labels the human genome as "the heritage of humanity" (Art. 1) and affirms that germline alterations could be regarded as "contrary to human dignity" (Art. 24). The following year, the United Nations General Assembly formally endorsed the Declaration. Also in 1997, the Council of Europe opened for signature the *Convention on Human Rights and Biomedicine* (Oviedo Convention), which is at present legally binding for 29 European states (including Switzerland). The Convention forbids interventions on the human genome that aim "to introduce any modification in the genome of any descendants" (Art. 13). Similar statements can be found in other international recommendations and guidelines from various governmental and non-governmental bodies, as well as in many domestic legislations.[1] Hence, it can be claimed that the ban on germline alterations has become over the years a principle of international biolaw [8].

This issue of *Bioethica Forum* is specifically focused on genome editing in humans. Many of the contributions deal with the ethical controversies surrounding human germline modifications. The key questions that inform most of the contributions are: are there any circumstances in which editing human embryos could be justified? More concretely, should the creation of genetically modified embryos be authorized when it aims to 'correct' genetic mutations predisposing to diseases, and the risk of harm to the offspring and their descendants is reduced to a minimum? Or are there reasons, principled or merely prudential, to consider alterations in the human germline as a threshold that should never

1 In Switzerland, this principle even has constitutional status as it is enshrined in Article 119, paragraph 2a, of the Federal Constitution, which provides that "all forms of cloning and interference with the genetic material of human reproductive cells and embryos are unlawful".

be crossed? Additional difficult questions that arise in this context are: can a risk that may unpredictably affect future people – either physically or psychologically – ever be regarded as 'minimal'? Is there any guarantee that inheritable genetic modifications, even if initially focused on improving health, will not start us down a path towards non-therapeutic design of future children? Another more fundamental question is: are we perhaps faced here with an ambivalence of another kind than that of previous technological developments? Previously, our technologies could indeed be used for good and bad purposes. However, we have always been free to renounce them when we notice that they may bring more harm than good (nuclear energy is a recent example of this). But germline genetic engineering is different in the sense that it aims at changing, not the *tools* that we use, but the *users* themselves (that is, ourselves, or rather, our descendants), and this in an irreversible manner. Is the classic risk–benefit analysis really applicable to this radically new scenario?

All these questions are extremely difficult to answer. What is clear is that bioethics has rarely been confronted with such challenging issues concerning our self-understanding as human beings and the long-term effects of our technological choices.

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