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Questioning the proposed translational pathway for germline genome editing

Despite opprobrium from the scientific community, the creation of the first CRISPR babies by germline genome editing has led to a debate more about execution than intent. We need public education, engagement and empowerment to reach 'broad societal consensus' on whether, not how, to pursue heritable genome editing, argues Françoise Baylis.

In late November 2018 the future came crashing into the present when Jiankui He, a researcher in Shenzhen, China, self-reported that he had created the world's first CRISPR babies. While many thought it was only a matter of time before this happened, few thought it would be this soon: only three-and-a-half years after researchers in Guangzhou, China, first reported the use of CRISPR technology to edit human embryos in the laboratory.

The global response to the unexpected news that supposedly healthy twin girls had been born from embryos genetically modified to confer resistance to HIV was swift and almost uniformly critical. In condemning He, a number of scientists were quick to distance themselves from this 'rogue' scientist and to reassure the general public that responsible scientists could, and would, do 'well' what He had done 'poorly'.

This response is disconcerting insofar as it suggests that the ethical issue with He's research was one of execution, not intent. And yet, the question about intent—is it ethical to proceed with human germline editing?—logically precedes the question about execution—how can we proceed ethically with human germline editing? Until the first question has been fully explored and authoritatively answered in the affirmative, the second question is moot.

Following He's surprise announcement, prominent scientists David Baltimore and Feng Zhang independently condemned He's research. In so doing, they both referenced the concluding Statement from the 2015 International Summit *On Human Gene Editing* (<http://www8.nationalacademies.org/onpinews/newsitem.aspx?RecordID=12032015a>), according to which it would be irresponsible to proceed with any clinical use of germline editing unless and until safety and efficacy is assured and a "broad societal consensus about the appropriateness of the proposed application" has been achieved.

Notwithstanding this clear admonition from Baltimore and Zhang, and the more general hue and cry that He had violated international

consensus, the concluding Statement from the Second International Summit *On Human Genome Editing* (held a few days after He's announcement) asserted that it is now "time to define a rigorous, responsible translational pathway toward such trials" (<http://www8.nationalacademies.org/onpinews/newsitem.aspx?RecordID=11282018b>). That the opprobrium directed at He should lend itself to this conclusion is both surprising and troubling.

Among the proposed criteria for acceptable germline genome editing, the 2018 Summit Statement listed "strict independent oversight, a compelling medical need, an absence of reasonable alternatives, a plan for long-term follow-up, and attention to societal effects." What this amounts to in practical terms, however, is most unclear.

What is the appropriate standard for "strict independent oversight" of germline genome editing? Jiankui He maintains that his research was reviewed and approved by the relevant institutional research ethics committee. This system of local (and, sometimes, voluntary) oversight has been common for CRISPR research involving human embryos. One exception to this practice is the research conducted by Kathy Niakan in the United Kingdom, where there is national mandatory oversight by the Human Fertilisation and Embryology Authority. Should national (or international) oversight replace local institutional oversight?

What is a "compelling medical need" for germline genome editing? According to He, HIV infection is a major problem in China, where it can have a devastating impact on quality of life because of stigma. Others, however, maintain that the risk of HIV infection is not an adequate medical indication. Meanwhile the US National Academies of Sciences, Engineering, and Medicine and the Nuffield Council on Bioethics suggest that the desire for healthy genetically related children by prospective parents who are at risk of passing on a serious genetic disease to their children is (might be) a compelling medical need. Who decides?

What is a "reasonable" alternative to germline genome editing? For example,

with respect to the risk of HIV infection, is sperm washing before IVF a reasonable alternative means of reproduction for prospective parents? And are safe-sex education and antiviral drugs reasonable alternatives for future offspring? Or, with respect to the risk of transmitting a serious genetic disease to one's children, are adoption, sexual reproduction followed by prenatal testing and abortion, IVF followed by pre-implantation diagnosis and embryo selection, or IVF using healthy donor sperm or eggs reasonable alternatives?

What is a sufficient "plan for long-term follow-up" of children born of germline genome editing? Parents cannot be forced to enrol their children in research for life (or even until the age of majority). And once the children are adults, they cannot be coerced into ongoing research participation. So, what kind of long-term plan would satisfy this requirement?

And finally, what does "attention to societal effects" of germline genome editing require? Public education? Public engagement? Public empowerment? For those of us committed to public empowerment, we can but insist on the importance of public education and public engagement in working toward a "broad societal consensus" on whether to pursue heritable human genome editing.

Until the first question has been fully explored and authoritatively answered in the affirmative, the second question is moot. □

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