Heritable genome editing not yet ready to be tried safely and effectively in humans

Heritable genome edits can be passed down to future generations, raising not only scientific and medical considerations but also a host of ethical, moral, and societal issues. Extensive societal dialogue is needed before any country decides whether to permit clinical use of heritable human genome editing - making alterations to genetic material of human eggs, sperm, or any cells that lead to their development, including the cells of early embryos - with the intention of establishing a pregnancy.

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If a nation decides that heritable human genome editing (HHGE) is permissible, initial uses should be limited to the prevention of serious monogenic diseases, which result from the mutation of one or both copies of a single gene — for example, cystic fibrosis, thalassemia, sickle cell anemia, and Tay-Sachs disease, a new report by an international commission of the US National Academy of Medicine, US National Academy of Sciences, and the UK's Royal Society.

For these cases, HHGE should only be considered when prospective parents who are at known risk of transmitting a serious monogenic disease have no option or extremely poor options for having a biologically related child who is not genetically affected without the editing procedure, due to genetic circumstances or the combination of genetic circumstances and fertility issues.

"Any initial uses of HHGE should proceed incrementally and cautiously, and provide the most favorable balance of potential benefits and harms. For the prevention of serious monogenic diseases, the commission has defined a responsible clinical translational pathway from rigorous preclinical research that determines whether and how editing can be performed efficiently and with high accuracy, to clinical application. Countries would then decide whether an editing application is permissible, informed by preclinical data as well as broad discussion of social and ethical issues. The report provides guidance on essential elements of national and international scientific governance and oversight," says Richard Lifton, commission co-chair president of the Rockefeller University, New York City.

At this time, it is not possible to define responsible translational pathways from research to clinical application for other potential uses of HHGE, the report says. The uses, circumstances, and considerations differ widely, as do the technical advances that would be needed to make additional clinical uses feasible.

“Should they ever be used, it is vitally important that these technologies are used for medically justified interventions, based on a rigorous understanding of how the pathogenic variant leads to disease.

“More research is needed into the technology of genome editing in human embryos, to ensure that precise changes can be made without undesired off-target effects. International cooperation and open discussion of all aspects of genome editing will be essential," says Kay Davies, commission co-chair and professor of genetics at the MDUK Oxford Neuromuscular Centre at the University of Oxford.

The international commission was formed in the aftermath of the 2018 International Summit on Human Genome Editing held in Hong Kong, where a researcher from China announced that twins had been born following editing he had performed on early embryos, despite broad agreement in the scientific and clinical communities that it was premature and irresponsible to undertake heritable human genome editing.

How a scientist says he made a gene-edited baby - and what health worries may ensue
George Seidel 3 Dec 2018

The commission — comprising 18 members from 10 nations with expertise in genome editing technology; human genetics and genomics; psychology; reproductive, pediatric, and adult medicine; regulatory science; bioethics; and international law — was tasked with developing a framework for scientists, clinicians, and regulatory authorities to consider when assessing potential clinical applications of heritable human genome editing. The commission’s goal was to define specific criteria and standards that would be required before HHGE could be considered for clinical use. The resulting report will inform the World Health Organisation’s expert advisory committee on human genome editing, which is developing appropriate governance mechanisms for both heritable and non-heritable human genome editing research and clinical uses. The WHO advisory committee is expected to issue its guidance later this year.

A translational pathway from research to clinical use

The translational pathway described in the report for initial clinical use of HHGE identifies a number of requirements for preclinical evidence that should be met to demonstrate with high confidence that embryos have been correctly edited as intended, before any attempt is made to establish a pregnancy with edited embryos. The in vitro development of edited human embryos should also be evaluated prior to establishing a pregnancy to ensure that they meet developmental milestones, comparable to those of unedited embryos resulting from current in vitro fertilisation practices. A biopsy should demonstrate that the intended edit is present in all biopsied cells, with no evidence of unintended edits. If, after rigorous evaluation, regulatory approval to establish a pregnancy is granted, monitoring the resulting pregnancy is vital, as is longer-term follow-up into adulthood of any children born.

Research should continue to evaluate the potential use of stem cells in producing functional human eggs or sperm, the report says. This technique could reduce or eliminate the need for genome editing at the time of or after fertilization.

However, this type of HHGE should be carefully evaluated, as it raises its own distinct medical, ethical, and societal issues. The technique would need to be approved for use in assisted reproductive technology before editing such germ cells could be considered for clinical use.

Scientific governance and oversight

Each nation that considers developing HHGE will draw on its own regulatory infrastructure and oversight authorities, but all countries in which HHGE is being researched or conducted should have mechanisms and regulatory bodies in place to oversee progress toward potential clinical uses, prevent unapproved uses, and sanction misconduct, the report says.

In addition, before any clinical use of HHGE, an independent, multidisciplinary International Scientific Advisory Panel should be established to continuously assess the state of the scientific evidence regarding safety and efficacy of both human genome editing and associated assisted reproductive technologies. The panel should assess whether preclinical requirements have been met, review data on clinical outcomes from any regulated uses of HHGE, and advise on risks and benefits of other potential applications. Furthermore, it is very important that an international mechanism be established through which concerns about the ethics of research or conduct of heritable human genome editing that deviates from established guidelines or recommended standards can be reported to relevant authorities and publicly disclosed.

In order to proceed with any HHGE applications that go beyond the initial uses as described by the commission, the commission recommends the creation of an international body with appropriate standing and diverse expertise to make recommendations concerning any proposed new category of use, and to advise on scientific and clinical benefits and risks. Informed by the work of the International Scientific Advisory Panel, this body should enable and convene ongoing discussions on the societal issues surrounding potential new applications of HHGE.