Don’t edit the human germ line

Edward Lanphier, Fyodor Urnov, Sarah Ehlen Haecker, Michael Werner & Joanna Smolenski

12 March 2015

Heritable human genetic modifications pose serious risks, and the therapeutic benefits are tenuous, warn Edward Lanphier, Fyodor Urnov and colleagues.

Subject terms: Biotechnology Therapeutics Ethics Policy

It is thought that studies involving the use of genome-editing tools to modify the DNA of human embryos will be published shortly.

There are grave concerns regarding the ethical and safety implications of this research. There is also fear of the negative impact it could have on important work involving the use of genome-editing techniques in somatic (non-reproductive) cells.

We are all involved in this latter area of work. One of us (F.U.) helped to develop the first genome-editing technology, zinc-finger nucleases\(^2\) (ZFNs), and is now senior scientist at the company developing them, Sangamo BioSciences of Richmond, California. The Alliance for Regenerative Medicine (ARM; in which E.L., M.W. and S.E.H. are involved), is an international organization that represents more than 200 life-sciences companies, research institutions, non-profit organizations, patient-advocacy groups and investors focused on developing and commercializing therapeutics, including those involving genome editing.
Genome-editing technologies may offer a powerful approach to treat many human diseases, including HIV/AIDS, haemophilia, sickle-cell anaemia and several forms of cancer. All techniques currently in various stages of clinical development focus on modifying the genetic material of somatic cells, such as T cells (a type of white blood cell). These are not designed to affect sperm or eggs.

In our view, genome editing in human embryos using current technologies could have unpredictable effects on future generations. This makes it dangerous and ethically unacceptable. Such research could be exploited for non-therapeutic modifications. We are concerned that a public outcry about such an ethical breach could hinder a promising area of therapeutic development, namely making genetic changes that cannot be inherited.

At this early stage, scientists should agree not to modify the DNA of human reproductive cells. Should a truly compelling case ever arise for the therapeutic benefit of germline modification, we encourage an open discussion around the appropriate course of action.

Editing tools
Genome editing of human somatic cells aims to repair or eliminate a mutation that could cause disease. The premise is that corrective changes to a sufficient number of cells carrying the mutation — in which the genetic fixes would last the lifetimes of the modified cells and their progeny — could provide a ‘one and done’ curative treatment for patients.

For instance, ZFNs are DNA-binding proteins that can be engineered to induce a double-strand break in a section of DNA. Such molecular scissors enable researchers to ‘knock out’ specific genes, repair a mutation or incorporate a new stretch of DNA into a selected location.

Sangamo BioSciences is conducting clinical trials to evaluate an application of genome editing as a potential ‘functional cure’ for HIV/AIDS. The hope is that intravenous infusion of modified T cells will enable patients to stop taking antiretroviral drugs. A phase I trial in patients with β-thalassaemia — a genetic blood disorder caused by insufficient haemoglobin production — is scheduled to begin this year.

The newest addition to the genome-editing arsenal is CRISPR/Cas9, a bacteria-derived system that uses RNA molecules that recognize specific human DNA sequences. The RNAs act as guides, matching the nuclease to corresponding locations in the human genome. CRISPR/Cas9 is the simplest genome-editing tool to work with because it relies on RNA–DNA base pairing, rather than the engineering of proteins that bind particular DNA sequences.

“The precise effects of genetic modification to an embryo may be impossible to know until after birth.”

The CRISPR technique has dramatically expanded research on genome editing. But we cannot imagine a situation in which its use in human embryos would offer a therapeutic benefit over existing and developing methods. It would be difficult to control exactly how many cells are modified. Increasing the dose of nuclease used would increase the likelihood that the mutated gene will be corrected, but also raise the risk of cuts being made elsewhere in the genome.

In an embryo, a nuclease may not necessarily cut both copies of the target gene, or the cell may start dividing before the corrections are complete, resulting in a genetic mosaic. Studies using gene-editing in animals such as rats, cattle, sheep and pigs, indicate that it is possible to delete or disable genes in an embryo — a simpler process than actually correcting DNA sequences — in only some of the cells.

The current ability to perform quality controls on only a subset of cells means that the precise effects of genetic modification to an embryo may be impossible to know until after birth.
embryo may be impossible to know until after birth. Even then, potential problems may not surface for years. Established methods, such as standard prenatal genetic diagnostics or *in vitro* fertilization (IVF) with the genetic profiling of embryos before implantation, are much better options for parents who both carry the same mutation for a disease.

**Legal case**

Patient safety is paramount among the arguments against modifying the human germ line (egg and sperm cells). If a mosaic embryo is created, the embryo’s germ line may or may not carry the genetic alteration. But the use of CRISPR/Cas9 in human embryos certainly makes onward human germline modification a possibility. Philosophically or ethically justifiable applications for this technology — should any ever exist — are moot until it becomes possible to demonstrate safe outcomes and obtain reproducible data over multiple generations.

Because of such concerns — as well as for serious ethical reasons — some countries discouraged or prohibited this type of research a decade before the technical feasibility of germline modification was confirmed in rats in 2009 (ref. 9). (Today, around 40 countries discourage or ban it.)

Many countries do not have explicit legislation in place permitting or forbidding genetic engineering in humans — considering such research experimental and not therapeutic (see go.nature.com/uvtlmu). However, in nations with policies regarding inheritable genetic modification, it has been prohibited by law or by measures having the force of law.

This consensus is most visible in western Europe, where 15 of 22 nations prohibit the modification of the germ line4. Although the United States has not officially prohibited germline modification, the US National Institutes of Health’s Recombinant DNA Advisory Committee explicitly states that it “will not at present entertain proposals for germ line alterations” (see go.nature.com/mgscb2).

In general, researchers who want to investigate the clinical uses of genetically engineered somatic cells must secure people’s informed consent. In the United States, this takes place under the oversight of the Food and Drug Administration and the Department of Health and Human Services. For research involving genetic modification of the germ line, it is unclear what information would be needed — or obtainable — to adequately inform prospective parents of the risks, including to future generations.

Many oppose germline modification on the grounds that permitting even unambiguously therapeutic interventions could start us down a path towards non-therapeutic genetic enhancement. We share these concerns.

**Dialogue needed**

Ten years ago, the Genetics and Public Policy Center, now in Washington DC, brought together more than 80 experts from the United States and Canada to consider the scientific and ethical consequences of genetically modifying the human germ line. Now that the capability for human germline engineering has emerged, we urge the international scientific community to engage in this type of dialogue. This is needed both to establish how to proceed in the immediate term, and to assess whether, and under what circumstances — if any — future research involving genetic modification of human germ cells should take place. Such discussions must include the public as well as experts and academics.

An excellent precedent for open, early discussion as new scientific capabilities emerge was set by the hearings, consultations and reports involving scientists, bioethicists, regulators and the general public that preceded the UK government’s decision to legalize mitochondrial DNA transfer in February. We are not, of course, making a comparison between the replacement of faulty mitochondrial DNA in an egg or embryo with healthy DNA from a female donor and the use of genome-editing in human embryos. In mitochondrial transfer, the aim is to prevent life-threatening diseases by replacing a known and tiny fraction of the overall genome.

Key to all discussion and future research is making a clear distinction between genome editing in somatic cells and in germ cells.
A voluntary moratorium in the scientific community could be an effective way to discourage human germline modification and raise public awareness of the difference between these two techniques. Legitimate concerns regarding the safety and ethical impacts of germline editing must not impede the significant progress being made in the clinical development of approaches to potentially cure serious debilitating diseases.


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Competing financial interests
E.L. and F.U. are employees of Sangamo BioSciences, Inc.

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11 comments

mark miller · 2015-04-21 11:24 PM
"Such research could be exploited for non-therapeutic modifications. We are concerned that a public outcry about such an ethical breach could hinder a promising area of therapeutic development, namely making genetic changes that cannot be inherited." The same could be said of nuclear fission. Any nation that wants it badly enough has gotten it. This technology doesn't require state actors to fully exploit it. So the probability that it will not be used for non-therapeutic modifications is negligibly close to zero. Further more, as most of us suspect and will soon know, the Chinese have a vastly different attitude toward the prospect of human self-improvement at the germ line level. Any outcry from Westerners will be duly noted and utterly ignored. So, then, what is the concern really of the authors? That the technology will not be effective or, as I suspect, that the technology will be too effective, laying to rest once and for all the "tabula rasa" narrative of the Left?

Dan Gibbs · 2015-03-27 11:15 PM
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Don’t edit the human germ line: Nature News & Comment

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Paul Watson • 2015-04-14 06:59 PM

Engineering for increased prosociality would be likely to ameliorate the situation pointed out by Dan Gibbs, above -- a wonderful side benefit to enhanced species sustainability. This also gives me the chance to emphasize that engineering for increased prosociality and biophilia would involve providing (given needed research funding) genetic fixes for all "normal" humans. The fixes need to be pan-cultural, pan-ethnic, etc. We are dealing with species-typical traits that make virtually all of us not care enough about the welfare of other humans, not care enough about pollinators in crisis, etc., etc...

Paul Watson • 2015-03-24 06:36 PM

All the authors’ concerns are totally valid, IMO, and I am strongly in favor of the moratorium, especially as regards germ-line genomic modifications. However, I think that as we ramp up our ethical discussion on this topic, we urgently and soberly have to consider the following.

We are a congenitally unsustainable life form that causes untold suffering for fellow humans and countless other sentient beings. Ponder this: all technologically powerful life forms across the cosmos, to render themselves sustainable, probably have had to stop natural selection, our ever active default eugenist, from having its unhindered way with them, specifically in designing their brains and hence their emotions, moral deliberation processes, and their general grip on reality. We'll have to do the same to keep the human experiment running.

It's time we face the likelihood that, as we are genetically constituted, we will continue to be a ruthlessly tribal, resource and power-grabbing, warring, extinction-bound species. Yes, we need to develop the strongest possible ethical and scientific framework for editing human genes. As part of this effort it is crucial that we consider our socioecologically grave and urgent situation.

Humans are amazing, wonderful creatures. But, there's a fact we must face, and now is the time. Having been designed
by natural selection, our unconscious, pan-cultural "prime directive" is to maximize individual lifetime inclusive fitness; this means that the unconscious drive to transmit our genes to future generations, using an incredible variety of direct and indirect strategies, often including impressive albeit ruthlessly contingent, more or less parochial altruism, trumps and "poisons everything." It is why we are so good at causing suffering for our fellow humans and the other creatures with whom we "share" the Earth, all the while proceeding to cause a global, soon-to-be irreversible "Tragedy of the Commons." It is why our heartfelt "real" higher values are expressed mainly in ways that directly and indirectly (e.g., via helping our supporting in-group) attain fitness-enhancing goals.

Culture, that is, socioecological changes we come up with through the outputs of our naturally selected minds, seems unlikely to save us, although innovative strategies obviously should be tried, along with less onerous epigenetic engineering. However, the developing genetic editing tools that scientists and bioethicists so rightly worry about probably are our principle long term way out of this trap. They offer up the miraculous and pivotal opportunity for humankind to bring about a new age of "intentional evolution," ethically aimed at the rendering ourselves fundamentally more prosocial, biophilic, and ecologically viable. These, I offer, are the traits that should be at the top of the list for "tuning up" via somatic or germ-line editing.

mark miller  •  2015-04-21 11:27 PM
Do you think any prospective moratorium will have more effect than, say, the Bush moratorium on stem cell research? It will simply accelerate China's dominance in the field. Transglobal elites will happily consume the service without regard to the flag it may be flying under. So in that light, by all means, I'm for a moratorium as well.

PJ Northway  •  2015-03-20 04:47 PM
I call for a moratorium on moratoriums. There has been VERY little, if any, informed Public debate on ANY aspect of Genetics, much less ground breaking germ line editing. There ARE serious ethical challenges inherent in the processes and outcomes, but typically debate consists of pat answers and excuses, "We shouldn't play God" and that sort of thing. We "play God" every, single day. We choose who has resources and who does not; who goes to War and who does not; we experiment with the Climate, Earth, Air and Water almost daily. Genetic code is modified by a torrent of untested chemicals and industrial processes and by-products. The Hallmark of the Anthropocene IS Human Experimentation on a mass scale AND experimentation on Species that have no choice whatsoever.

Heeyoun Bunch  •  2015-03-18 01:37 PM
In my knowledge, risks of inheriting an edited (deleted) chromosome/gene haven't been rigorously tested throughout multiple generations. Editing embryonic cell may benefit that particular individual (if it is disposed to a certain, life-threatening genetic disease) but there is no guarantee of not having destructive consequences or problems in a long run from inheriting permanently modified genome. Considering the complexity of interwound cellular processes, editing a genome seems to be 'taking a quick, easy way'---but we know that it is not always wise.

Stephen Wilson  •  2015-03-16 06:52 PM
I am not a geneticist but a software professional and scientist. The genes-as-software parallel is widely cited but what's not properly appreciated is the way software is verified. Complex software cannot be empirically tested and, I suggest,
neither can the products of genetic editing. In software, it is received wisdom that most bugs result from imprudent changes made to existing programs. Furthermore, editing one part of a program can have unpredictable and unbounded impacts on any other part of the code. Input complexity means that all but the very simplest software is empirically untestable. So mission critical software (like the implantable defibrillator code I used to work on) is always verified by a combination of methods, including unit testing, system testing, design review and painstaking code inspection. Because most problems come from human error, software excellence demands formal design and development processes, and high level programming languages, to preclude subtle errors that no amount of testing could ever hope to find. How many of these software quality mechanisms are available to genetic engineers? Code inspection is moot when we don’t even know how genes normally interact with one another. Only recently was it found that junk DNA is not entirely junk. Geneticists obviously have an incomplete understanding of how genes interact. If we don’t actually know how one "line" of genetic code impacts the rest of the "program", how can we possibly tell by inspection if an edited gene will interfere with the "legacy" code? I’d say a moratorium is absolutely justified until such time as genetic "engineering" can rest on complete genetic science.

Bruce Bowen  ·  2015-03-13 11:04 PM
Once the techniques for converting somatic cells into germ cells is perfected, this whole argument will be moot.

Mike B  ·  2015-03-12 09:36 PM
Calling for a discussion is different than calling for a moratorium. A moratorium creates a paradox: don’t do experiments on genome editing in germ cells until it can be proven (by experimentation) that it’s safe to do experiments on genome editing in germ cells. It seems what you are actually calling for is a discussion about the ethics of such research, along with tightly controlled experiments to elucidate the risks of genome editing in germ cells.

Paul Knoepfler  ·  2015-03-12 05:39 PM
The call for proactive discussion by diverse stakeholders seems sensible. Even though work toward heritable gene editing-based human genetic modification seems to be already ongoing in some quarters and its use may be inevitable raising the question of just how "proactive" these discussions would be, it is not too late for community-wide engagement to have major positive impact in charting the future course of research and implementation of this technology in humans. Readers may find this week’s interview with George Church to be of interest, http://www.ipscell.com/2015/03/georgechurchinterview/, as his viewpoints are distinct from these authors in some interesting ways that resonate.

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Nature  ISSN 0028-0836   EISSN 1476-4687