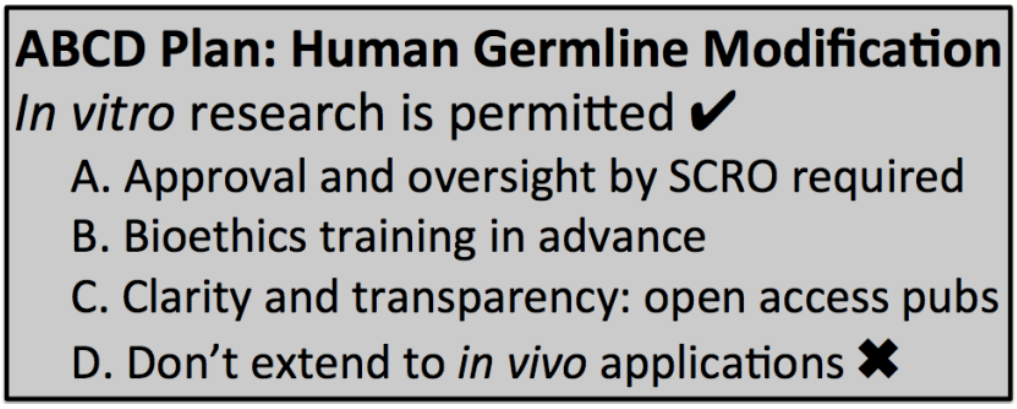
This response was submitted to the Call for Evidence held by the Nuffield Council on Bioethics on *Genome editing* between 27 November 2015 and 1 February 2016. The views expressed are solely those of the respondent(s) and not those of the Council.

On Genome Editing Call from Nuffield Council from Paul Knoepfler

How to manage human genetic modification?

CRISPR-Cas9 gene editing technology is a game changer on many levels both inside and soon outside the lab. There is a growing sense of urgency amongst biomedical scientists to take a proactive approach to current and future use of CRISPR technology in human germ cells and embryos.
These concerns have been heightened by rumors of multiple papers currently in various stages of peer review that will reportedly describe CRISPR-mediated gene editing of human embryos. A number of scientists and scientific organizations have recently come out with policy statements on human germline genetic modification: **Lanphier, et al. *Nature*, Baltimore, et al. *Science*,** and **ISSCR.**
I've outlined a proposed plan (see figure below) that I call ABCD for simplicity to try to practically manage the situation with human germline genetic modification. This plan shares a few key features with some of those already proposed by others, but in some ways it is different or more specific. This ABCD idea is just a possible plan coming from one person (me) with the intention of positively adding to the overall dialogue.



My view is that *in vitro* research on genetically modified human germ cells and early embryos–with appropriate training and oversight–is ethical and can in fact be of great value. Such work will provide new, valuable information about gene editing itself and early human development, fertility, and more. Therefore, such research should not be prohibited, but should only be conducted under certain conditions.

For example, the *In vitro* studies of genetically modified human germ cells and embryos would require appropriate **approval and oversight**. This is the **A part** of the plan. Given the urgency in terms of timing on this issue, it seems impractical to create new committees from scratch solely for this purpose. Thus, I propose that standing SCRO committees have the authority and responsibility to regulate genetically modified germ cell and embryo-related work. They already are the ones overseeing similar research now. The human germ cell and embryo CRISPR work would have to have a compelling justification to get SCRO approval.

Researchers proposing to the relevant SCRO or similar committee to conduct research related to human genetic modification of germ cells or embryos must also receive **bioethics training**, which is the **B part of the plan**. This is particularly important because of the complicated bioethical issues that this unique kind of work raises and such training would serve to provide a strong educational component. Bioethical issues to be discussed would include the human germ cell modification itself, the specific concerns over outcomes if the work were applied *in vivo*, and other aspects such as the sourcing of human oocytes. As to that last issue, *in vitro* CRISPR human genetic modification research could substantially increase the research demand for human eggs.

The **C part** of the plan is **clarity**. Both the public and scientists would greatly benefit from education and openness in this area. Transparency and outreach in lay terms is essential for public trust. Research on human germline genetic modification, including those manuscripts potentially currently in review, should be published in open access format to make the data fully available to society as a whole. No pay walls here. This area of research is too important and charged to block access.

The **D part** of the plan is **don't extend the work to *in vivo*** applications involving implantation of genetically modified human embryos. There should be a moratorium on this step given the major ethical and safety issues involved. Whether such a moratorium could ever be lifted is unclear and would depend on what the data that come in the next few years teaches us. Practically speaking the questions of how such a moratorium would work or be enforced are tough ones, especially if one intends to extend it internationally.

With these **ABCD** guidelines in place the goal would be that innovative, valuable research in this area could proceed in a responsible and ethical manner, while minimizing the risk of negative outcomes.

_Within just a year or two the knowledge base regarding CRISPR-based gene editing will be vastly increased. Further, in the same timeline additional next-generation CRISPR approaches will improve accuracy and introduce further refinements in the technology. Plans for managing germline human genetic modification may need to evolve as well. The ongoing dialogue that has ramped up recently already shows signs of having very positive impact and is likely to continue to do so as it proceeds.

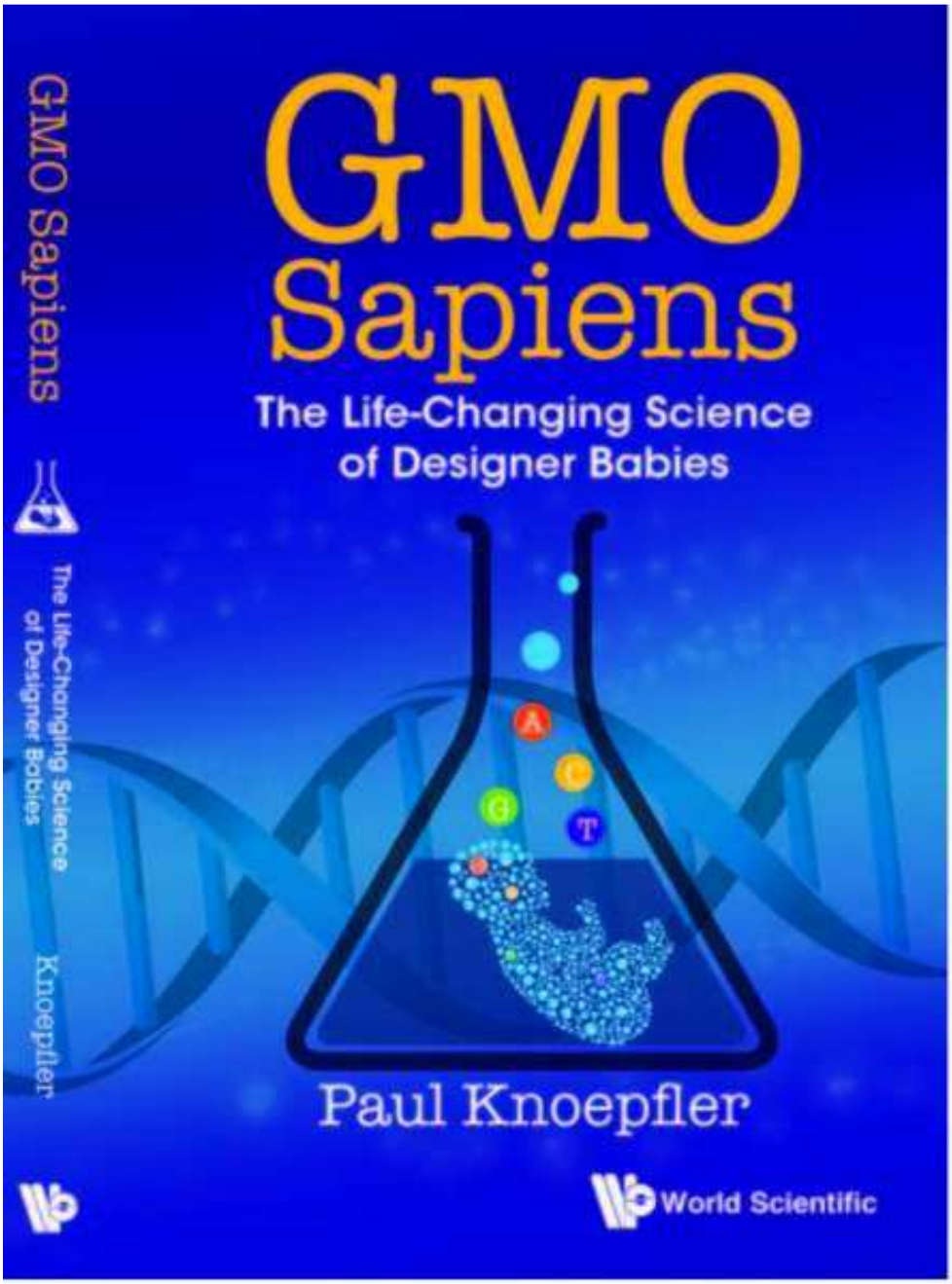
Should there be a moratorium?

I just got back from a historic summit on human genetic modification in Washington, D.C. New genetic modification technology, termed CRISPR-Cas9, has both made genetic modification a relatively simple matter for scientists and human genetic modification much more likely in the near future.

Heritable human genetic modification could prevent some rare genetic diseases so there is real potential there, but it also could open the door to serious problems such as unforeseen health consequences across generations, social justice issues, and eugenics. Both potential positives and negatives were discussed in depth at the summit. Keep in mind that most but not all genetic diseases already are preventable via existing technology that allows for genetic screening of unmodified human embryos.

I was there blogging the event (see posts **here**). My lab also works on genetics and genomics. We are using CRISPR for *in vitro* research on stem cells and cancer. The goal of the summit, held at the US National Academy of Sciences, was to chart a path forward on how science and scientists should handle the central question of whether to genetically modify humans and what considerations should go into such a decision.

The organizers of the summit tasked themselves more specifically with deciding whether to propose a moratorium on heritable human genetic modification. Several of them had in the previous months seemed to indicate support for something like a moratorium in public statements and interviews. However, at the end of the summit, **the organizer's statement** did not take a decisive step. They only discouraged heritable human genetic modification. There was no recommendation for a ban or moratorium.



In fact, David Baltimore who served as Chair, said at the end of the meeting that they specifically were not endorsing a moratorium and that was a conscious decision. It's not entirely clear though why they made this decision, which seems to leave the door somewhat open to making genetically modified humans. More on that in a bit.

My own perspective is that we need a moratorium of at least several years on clinical use of heritable human genetic modification technology so I am somewhat disappointed in the final summit statement.

Why am I concerned enough to be in favor of a clinical moratorium? I mentioned

some of the risks earlier in this piece. You also can see my concerns articulated in more depth in my new educational book on human genetic modification (**here**; note that it is written for both lay and scientific audiences and if you are interested in getting it you can use discount code WS15XMAS30 to get 30% off) and in **my new TEDxVienna talk**.

The summit organizers had several options available to them on their statement. You can think of it with a stoplight analogy. They could have proposed a moratorium, or a **red light**. They could have wholly endorsed human genetic modification and given it **a green light**. In fact the headline of a news story (see image above) seems to suggest that they did do this, but that is incorrect and the actual body of that article correctly reflects that the organizers only endorsed continuing basic research, which I also support.

Another option was to make a **yellow light** statement something along the lines of proceed with caution. They didn't do this either…at least not exactly. The organizers' statement was more like an "**orange light**", somewhere in between yellow and red. While they wrote that any attempts in the immediate future at heritable human genetic modification would be "irresponsible" they did not go so far as to say via a moratorium, "don't do it".

The vagueness to the public of the statement is further reflected in the fact that the headline of a story on the summit on the front page of the NY Times by Nicholas Wade got the gist of the summit statement exactly wrong and incorrectly said that the organizers did endorse a ban (see above).

Why did the organizers go for an orange light approach to germline human genetic modification?

Perhaps as a group this best represented their range of opinions. In other words, they themselves did not reach a consensus to have a moratorium. I didn't sense that there was such a consensus overall at the whole summit either. Reaching a consensus in science can be extremely challenging so by their nature consensus statements may tend not to be decisive. I get that.

One potential more practical reason for not proposing a moratorium is that the organizers firmly believe that germline human genetic modification will someday prove useful and desirable. I got that vibe from some of their talks as well as from those of other very influential parties at the meeting. In that hypothetical scenario, a moratorium today could be hard to reverse tomorrow (in the future). Perhaps they didn't want to risk impeding the clinical translation of the technology in the future with a moratorium. However, a pause in human genetic modification need not have been onerous or long-term.

Another possible consideration for the organizers is that a clinical moratorium could have hypothetically also unintentionally discouraged human embryo gene editing research in the laboratory so this may be another reason for not pursuing a moratorium. Again like the organizers, I also support such research, but for me it should be on a limited basis with appropriate bioethics training, transparency, and oversight (**see my ABCD plan**).

In the end, the statement from the organizers would have been more effective if it had been far shorter, clearer, and understandable to the lay public. Perhaps they were most focused on sending a message to scientists who might be more likely

to get the key points of the statement, but even so it would have been best to be understandable to all.
I hope that with continuing dialogue and meetings, which the organizers also rightly proposed, that this issue can be clarified further and that the public can be engaged at a far deeper level. However, there is strong urgency for action and clarity here, and the lack of a decisive statement from this unique meeting was a missed opportunity in that regard.
Time is short. The technology in this arena is advancing at warp speed, it is so ubiquitous, and there is such strong enthusiasm that we do not have the luxury of years to have more meetings and discussions, as much as they may be very important, without taking a clear stance.
The number one question I'm hearing today after the meeting is concerning: isn't human heritable genetic modification now already inevitable?

On gene drive in humans, animals, and potentially as weapon

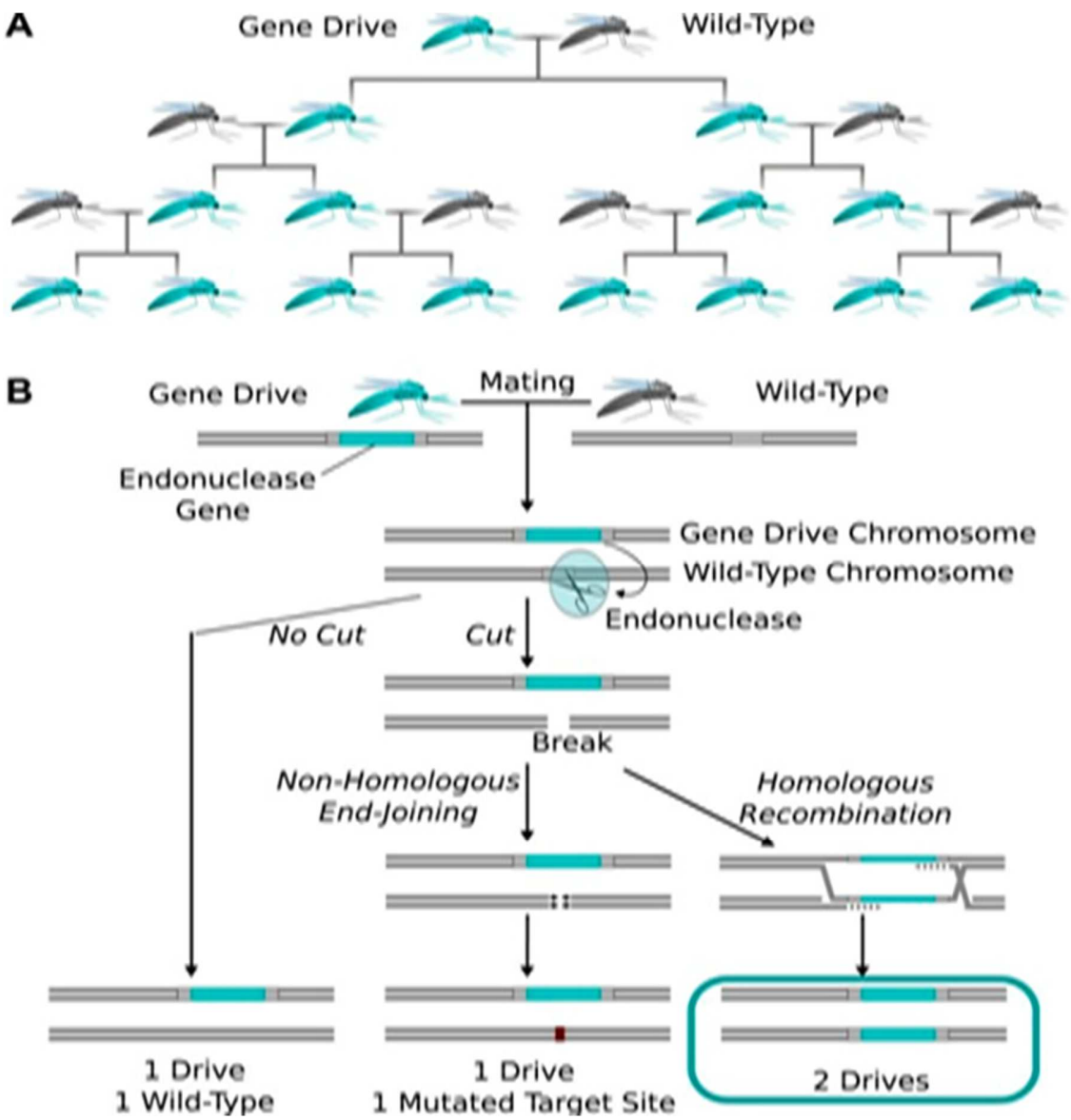
Scientists studying genetics are both excited and worried about a powerful, new technology called "gene drive. Some **have been raising** serious concerns about gene drive and in certain cases **calling for proactive regulation**, which is unusual in science.
Gene drive is so powerful because it is designed to induce genetic changes in an entire population in a relatively extremely short period of time compared to natural evolution and is self-propagating. The most talked about form of gene drive today is a type powered by CRISPR-Cas9 gene editing technology.
In principle, this kind of gene drive can be used both in research in the lab and out in the world depending on the desired application. During my 25 years in science, I' ve rarely seen scientists so excited and also this unsettled about a single technology. While potential

heritable genetic modification of human individuals via CRISPR is rightly generating substantial discussion, gene drive warrants increased attention and discussion because of its broad power and self-propagating nature. Within the lab, gene drive may make for more rapid, affordable, and in some cases elegant genetic experiments in model organisms. For instance, in mice the same kind of genetic experiments that could take years otherwise, may only take a few months if gene drive is utilized. This strongly resonates for me as a mouse genetics researcher. Gene drive can also be used in other model organisms such as fruit flies.

For hypothetical applications outside the lab, gene drive would take us into uncharted territory. It has been proposed to have great potential for health such as by targeting the mosquitoes that transmit malaria to humans and in agriculture by wiping out pests. A number of other hypothetical gene drive-based applications intended for real world implementation have been discussed. The only requirement for gene drive is that an organism reproduce sexually.

Gene drive works in a general sense by making a mutant gene be inherited more often than normal through an entire population. An engineered gene in a nuclease-driven gene drive system of the type powered by CRISPR-Cas9

might be inherited almost 100% of the time.
The more specific mechanism by which such a nuclease-driven gene drive works is by creating a mutant form of a gene that then itself also has the power (via CRISPR-Cas9 for instance) to change any additional WT copies of the gene that are present into gene drive mutants as well. In other words, a gene drive mutation has the ability to spread itself at the expense of normal WT copies of the same gene. For instance see Figure 1 from an intriguing **gene drive paper** from George Churchs group showing the possible spread of gene drive as represented by green mosquito symbols.



Eventually as gene drive continues there aren’ t many if any WT organisms left anymore. Much of the subsequent mating may occur between mutants and all offspring are mutants. The selfish gene drive wins out and in evolutionary terms this happens at warp speed. In a sense it is a genetic

chain reaction and one that it might be difficult for us scientists to control out in the field.

In the lab such a change may save researchers months or years of work compared to using now considered to be old-fashioned methods. In the real world, a gene drive could complete a genetic change in a population over a period of only months or years that might have naturally taken evolution millions of years. Of course, due to the artificial nature of this genetic change, something similar may never have occurred due to natural evolution. Imagine for real world applications if you could change a wild population of mosquitoes genetically such that they cannot be infected by Malaria and in turn they cannot infect people? Millions of lives could be saved.

Sounds amazing, right?

However, scientists are at least as worried about gene drive as they are excited.

Attempts at using gene drive to make ecosystem-wide genetic changes could prove extraordinarily risky for a variety of reasons. The first level of concern is over the sheer power and potential for speedy population-wide changes via fairly basic gene drives that hundreds or thousands of researchers could easily make in their labs today. The fact that gene drives are remarkably simple to engineer contrasts with the enormous complexity of how

biological and genetic systems function as well as the possibility of unexpected and enormous negative consequences to gene drives run amok. For instance, if a problem manifested in rapidly reproducing, mobile insects due to use of gene drive, there might well be almost nothing that scientists could do to stop the gene drive chain reaction from spreading.

Potentially stringent confinement strategies for gene drive research

TYPE	STRINGENT CONFINEMENT STRATEGY	EXAMPLES
Molecular	Separate components required for genetic drive Target synthetic sequences absent from wild organisms	sgRNA and Cas9 in separate loci (*8*) Drive targets a sequence unique to laboratory organisms (*3*,*4*,*8*)
Ecological	Perform experiments outside the habitable range of the organism Perform experiments in areas without potential wild mates	*Anopheles* mosquitoes in Boston *Anopheles* mosquitoes in Los Angeles
Reproductive	Use a laboratory strain that cannot reproduce with wild organisms	*Drosophila* with compound autosomes*
Barrier	Physical barriers between organisms and the environment •Remove barriers only when organisms are inactive •Impose environmental constraints •Take precautions to minimize breaches due to human error	Triply nested containers, >3 doors (*6*) Anesthetize before opening (*6*) Low-temperature room, air-blast fans Keep careful records of organisms, one investigator performs all experiments (*6*)

*An example of reproductive confinement would be *Drosophila* laboratory strains with a compound autosome, where both copies of a large autosome are conjoined at a single centromere. These strains are fertile when crossed inter se but are sterile when outcrossed to any normal or wild-type strain because all progeny are monosomic or trisomic and die early in development.

Even gene drive work intended to be limited to the lab has people very concerned. Model organisms such as fruit flies or mosquitoes that bear gene drive and are part of lab experiments could escape into the real world and mate with their wildtype counterparts. One analogy for this is a potentially toxic, genetic “spill” that is in a sense

infectious and self-perpetuating. Many bio-containment and other precautions have been proposed to avoid this situation by keeping gene drive organisms in the labs where they belong, but accidental release of gene driven organisms is a very real possibility.

Enabled by the simplicity and power of CRISPR-Cas9, many labs around the world may start making gene drive organisms without being fully aware of the risks. **Akbari and colleagues** have made a table (above) summarizing some proposed measures put forth collectively by the field to try to reduce this kind of risk as well as risks of actual intentional experiments in the field.

I recently talked with leading geneticist Harmit Malik, who I first met when I was a postdoc at the Hutch in Seattle, about concerns over gene drive. I hope to post this discussion in the near future. His perspectives on this important topic are very insightful and interesting.