Perspectives on genome modification

***What obligations do scientists involved in developing and using genome editing technologies owe to society and what freedoms should society allow to these scientists? Do genome scientists have any special obligations to society that are distinct from those of other scientists?***

The alliance between scientists and society is founded on mutual respect and trust. This traditional relationship is about to be subjected to severe stress.

Society relies on unbiased expert advice to help guide decisions as to how new technologies will ultimately be used. Scientific community members are actively working to explain the new genomic modification technologies, their potential benefits and some of the dilemmas ahead to the general public, funding agencies and government officials. In addition, well balanced articles on the promise and potential problems of gene drives have been published by scientists seeking to proactively inform colleagues and the general public about this facet of genomic engineering (http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4117217/). Despite these laudable efforts, it is not clear how well the involved scientists are meeting a responsibility to act as true honest brokers. One glaring problem is that many distinguished scientists at the center of discussions have strong vested professional and financial interests in seeing genomic editing research and development continue unimpeded (http://www.nature.com/news/gene-editing-record-smashed-in-pigs-1.18525; http://www.nature.com/news/genome-editing-7-facts-about-a-revolutionary-technology-1.18869). In addition, respected, high-profile science journals doing diligent and balanced reporting on the new technologies have also featured opinion pieces from key scientists which lacked any declarations of their directly competing interests (http://www.nature.com/nature/journal/v528/n7580_supp/full/528S7a.html). It is clear that for many scientists involved in gene editing technologies career advancement, prestigious awards and potentially enormous personal fortunes are all on the line, suggesting that the public debates to come are liable to become heated. Indeed, despite an almost total absence of reliable information regarding efficacy, gene drive proponents have already unleashed aggressive *ad hominem* attacks on anyone with doubts over releasing mechanisms to permanently alter the genetic composition of entire ecosystems (https://www.geneticliteracyproject.org/2015/12/09/white-privilege-will-western-activists-block-crispr-solution-protecting-millions-africans-malaria/#.VmtHvXxla0s.twitter).

Scientists should be mindful it is evident the new technologies have gotten well ahead of them. The emergence of operational CRISPR/Cas9-based genome editing technology and its utilization in many laboratories precipitated a public relations crisis. Recognizing an impending collision between swift scientific advancements and moral/ethical precepts held by many in the general public, a group of distinguished scientists called for a moratorium on experiments until the critical technical and ethical issues are examined. Unfortunately, rapidly unfolding breakthroughs have left the scientific community racing to establish guidelines for the responsible use of genome editing techniques while simultaneously attempting to explain the impacts of new technologies to the public.

***What obligations do governments have towards society to ensure 'safe' science or otherwise to shape the scientific research and development?***

Government(s) must assert its authority to act in the greater public interest in all aspects of decisions to enable, direct and regulate gene editing technologies. It is absolutely clear that many academic scientists at the forefront of gene editing research are also deeply involved in private sector efforts to commercialize the technologies. This group of scientists will almost certainly have an outsized influence on the development of critical guidelines for future research and deployment of gene editing techniques. In such complex circumstances government officials and agencies must act as the neutral judges of the costs, benefits and the true public interests served in permitting, or declining to permit, the use of genomic editing technologies.

Unless the thorny issues ahead are handled with the utmost of care and forethought, the public could easily lose confidence in both some of their most prominent scientists and the government. What constitutes 'safe' science? The answers, provided by scientists, vary. In the U.S. an embarrassing controversy erupted over the modification of H5N1 influenza ('bird flu') to forms that may have been able more readily to infect humans via a respiratory route. Although the investigators had conducted their work responsibly under strict biocontainment conditions, pointed questions concerning the value and wisdom of such efforts led to a public debacle over when and how the results should be published. A prohibition on publication was quickly reversed (http://www.sciencemag.org/content/336/6077/19.full?sid=21a8243c-793d-4f2a-baf4-01c844aab901), but a protracted battle was inflamed by intemperate public statements from both sides and threats issued by one scientist (http://www.nature.com/news/mutant-flu-researcher-plans-to-publish-even-without-permission-1.10469). This sad sequence of events revealed not only the fact that the scientists were having problems reaching a self-governing accord on fundamental safety issues, it was also not clear who made the final decisions. Hopefully, the governmental agencies and officials tasked with overseeing genetic editing technologies will adopt structures that are far more transparent and less subject to external pressures (http://www.sciencemag.org/content/335/6071/899.full?sid=3fbc10b4-4a30-4f5b-b276-5c78753a05b3).

The bird flu fiasco involved a matter that is far simpler than the situations emerging with gene editing technologies. That disagreement involved experiments conducted in a limited number of highly specialized research facilities and funded by a U.S. federal agency. In contrast, gene editing research is now being performed in many nations while multiple private sector corporations are making enormous capital investments in developing these technologies. Unless governments assert clear oversight authority over the basic directions of all research and development, potential clashes may make it impossible to realize the enormous benefits of gene editing technology.

## Genome editing in animals

***Are gene drives an area of particular interest or concern and, if so, why?***

Few areas could offer a better example of the accelerating pace of change characterizing genome editing technology than gene drives. Gene drives are of particular concern because this technology has progressed in a matter of months from theoretical

concept to ready-for-deployment constructs. Designed to combat significant threats to human health such as malaria, dengue, West Nile encephalitis and Lyme disease (http://www.npr.org/sections/health-shots/2015/11/05/451216596/powerful-gene-drive-can-quickly-change-an-entire-species), the pressure to unleash gene drives may be immense.

Some proposed uses of gene drives appear to be high-tech solutions in search of problems. For example, two serious human afflictions under consideration for gene drive mitigation are Lyme disease and Dengue. However, Lyme disease is preventable by taking measures to avoid the tick vectors and treatable with antibiotics while a new vaccine against Dengue just received approval for use in Mexico (http://www.sanofipasteur.com/en/articles/dengvaxia-world-s-first-dengue-vaccine-approved-in-mexico.aspx). A vaccine for Lyme disease was once produced commercially but was removed from the market due to insufficient consumer demand (http://www.cdc.gov/lyme/prev/vaccine.html). In these specific instances the deployment of gene drives seems unwarranted.

Falciparum malaria has been more intractable to medical interventions which makes it a more reasonable target for the use of gene drives. One strategy to render populations of the dominant vector mosquito species sterile by unleashing gene drives is already laboratory tested (http://www.nature.com/news/gene-drive-mosquitoes-engineered-to-fight-malaria-1.18858). Whether this approach will actually succeed in suppressing malaria transmission in complex natural ecosystems, if such interventions generate long-lasting benefits and are economically feasible compared to providing mosquito netting and eliminating vector breeding sites is unknown. Unfortunately, some adamant gene drive use proponents are oversimplifying issues (https://www.geneticliteracyproject.org/2015/12/09/white-privilege-will-western-activists-block-crispr-solution-protecting-millions-africans-malaria/#.VmtHvXxla0s.twitter) which call for careful deliberation and valid assessments of costs and benefits.

Gene drive proponents maintain that emergent undesirable impacts could be reversed through the agency of second drives or that it would be feasible to immunize target populations against constructs discovered to exert undesirable impacts. These attempts to downplay concerns about potentially deleterious gene drive impacts are preposterous; the proffered solutions are cascading hypotheses, not *bona fide* remediation strategies. Whether any gene drives will succeed in the wild remains unproven. Whether a second gene drive developed to antagonize a precursor will be able to achieve the practical goal of elimination is even more hypothetical. Although it is easy to contrive theoretical solutions to problems following the release of a gene drive, it is clear that the consequential negative ecological impacts produced by them might be difficult or impossible to reverse. In addition, these hypothetical correction measures fail to take into account the regulatory processes that will likely be involved with any future releases of gene drives. Will attempted erasures receive fast-track regulatory approval? Scientists involved with gene drive research must have some awareness of regulatory hurdles involved. Glib statements and half-baked strategies serve no useful scientific purpose and may be taken by some as deliberately deceptive.

***What other important questions should or might we have asked in this section?***

*How will risk assessments for proposed gene drive releases be conducted and the corresponding results conveyed accurately to the general public and decision makers?*

Gene drives will be released into dimly understood and dynamic natural environments. Assessing their risks and impacts will pose significant challenges.

Scientific advancements reduced to clinical medical practice have yielded tremendous human health benefits. For example, recognizing the existence of blood groups set the stage for safe transfusions and other life-saving interventions. However, these aggressive treatments also convey some risks. Their wide adoption also promoted the inadvertent, swift and broad dissemination of pathogens such as hepatitis viruses (HBV and HCV) and human immunodeficiency viruses (HIV) (http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1904179/). The mad cow disease (bovine spongiform encephalopathy, BSE) epidemic (http://www.bseinfo.org/AboutBSE.aspx) followed a simple operational change that at first consideration reasonably seemed to have posed no risks to either animal or human health. The practice of feeding meat bone meal offal back to cattle amplified pathologic prions and ultimately produced a catastrophic epidemic of BSE. The almost simultaneous appearance of a novel disease, new variant Creutzfeldt-Jakob disease, vCJD, in the same locality was recognized after some delay to be the harbinger of a substantial human health threat. The direct economic losses to the British cattle industry were devastating, the extent of the ultimate threat to the blood supply and human health are still being assessed over 25 years later.

For those who would use gene drives, past experience should be humbling confirmation that our assessments of both benefits and adverse outcomes have sometimes been seriously deficient. When scientists declared that antibiotics heralded the end of infectious diseases, we learned about formerly unsuspected resistance mechanisms and genetic exchange processes among microbes. When humans altered natural environments using chemical pesticides, herbicides and insecticides, we learned hard lessons about bio-magnification. The temptations to use gene drives to accomplish remarkable feats will be immense. But these future engineers will be facing true black box functionality, meaning risk assessments will be predicated on limited information. Is it reasonable to believe we will be able to project all impending issues or detect unanticipated consequential changes that only emerge after extended periods in time to control or reverse them?

*How will future gene drive engineers ensure public safety if unforeseen adverse events emerge?*

Paralytic poliomyelitis was once termed infantile paralysis because it was a rare disease of children. However, public health improvements such as the provision of clean drinking water set the stage for the large polio epidemics that began in the 19$^{th}$ century. Clean water saved many from scourges such as cholera and typhoid fever, but it also allowed large numbers of children to escape the once virtually inevitable poliovirus infections during infancy. Unfortunately, delaying the age of first contact with polioviruses meant that these infections were far more likely to leave their victims paralyzed. Poliomyelitis is sometimes referred to as a 'civilization disease' to reflect this unanticipated and tragic sequence of events (http://www.smithsonianmag.com/science-nature/conquering-polio-79115957/?sessionGUID=a7521aa9-062e-8399-9a57-38a3d0a10890&no-ist=&page=7). Clearly, no one would argue that to prevent polio we should return to a situation in which people drink polluted water. The remedy for surging polio epidemics was the mass immunization programs started in the 1950's and continuing today. What we do need to bear in mind is that simple, obviously beneficial changes sometimes have entirely unanticipated consequences. We may be able to solve the original issues completely only to see totally new concerns appear.

Foes of gene drive use seem unlikely to prevail using arguments predicated on fears something unknown might happen. Proponents will probably assail the precautionary principle and some are already complaining that risks associated with genome editing technologies are not novel and talks should focus on the benefits (http://www.nature.com/nature/journal/v528/n7580_supp/full/528S7a.html). However, it will be impossible to forecast all outcomes and every consequential response from complex ecosystems subjected to gene drive manipulation. Obvious safety gaps have led scientists to proactively engineer safer gene drives (http://www.sciencemag.org/content/349/6251/927.long) and tout putative remediation strategies (http://www.nature.com/nbt/journal/vaop/ncurrent/full/nbt.3412.html) such as releasing a second gene drive to overwrite released constructs creating problems. The situation suggests that in addition to planning to mitigate foreseeable adverse impacts, future ecosystem genetic engineers must develop specific, proven capacities to reverse their proposed alterations in the event undesirable consequences emerge. In addition, engineers must create long term monitoring plans for gene drive altered ecosystems to reveal any adverse impacts.

Perhaps the future global standard of ecosystem care will demand engineers devise interventions that impose the least possible degree of permanent perturbation. Although there seems to be a strong presumption of use, for some goals such as human disease control unleashing gene drives might actually be a less effective and more time-consuming approach than other low-tech methods. The most problematic uses of gene drives are those with impacts that definitely carry forward into the future. However, for many diseases it is feasible to break the chain of transmission without permanently fracturing the backbone of the ecosystem genetic network. For example, precisely targeted tools like ONRAB or Raboral V-RG can control rabies without any genetic legacy effects by vaccinating wild animal reservoirs. Perhaps the least risky first deployments of genetically modified wild organisms might be to emulate the Oxitec strategy to modulate mosquito vector populations (http://www.oxitec.com/). Analogous to the sterile insect methods used in the past to interrupt pest reproduction, this approach could harness the potential of genetic methods to achieve specifically aimed impacts without permanently modifying the genetic information of the targeted population.

*How will gene drive control measures targeting invasive species be restricted to locales in which the organisms are problematic?*

Using gene drives to extirpate invasive organisms may offer a unique solution to a serious global ecological problem. However, this tactic is not risk free. Plans must be developed to ensure the gene drive is permanently excluded from the native habitat of the intended target because unless the gene drives are well controlled extirpation could quickly become extinction. Although gene drives may be used to great advantage to control invasive species, it may turn out to be much easier to make grand promises to the public than to actually keep them.

*What sort of public discussions do gene drive proponents seek to foster?*

I urge my colleagues to think carefully about their words and actions. A distinguished scientist has noted that gene drive technology "… is potentially a way for us to interact with nature in a whole new way — using biology rather than bulldozers and toxic pesticides" (http://www.npr.org/sections/health-shots/2015/11/05/451216596/powerful-gene-drive-can-quickly-change-an-entire-species). However, it is important to recognize that society faces no such dire dichotomy.

Clearly, controlling diseases such as malaria is a moral imperative. However, the strategies adopted and how they are sold to the public must be realistic and truthful. No formal plans have been developed, no credible field tests have been conducted, no one can be certain the approach will actually work or be feasible to implement while gene drive proponents seem to be oversimplifying the issues. For example, malarial parasites are adapted to survive in multiple host species which actively resist them. Whether alterations to mosquito hosts conveyed by gene drives will ever be able to cope with such an elusive parasite remains uncertain. Whether conceptually more straightforward strategies to simply drive vector species to local extinction will work in natural ecosystems must be determined. However, past experience suggests we will do well to attack any diseases as ecologically and functionally complex as malaria from several angles and be scrupulous in revealing the full spectrum of difficulties involved to the general public. I ask those who propose using gene drives to 'eliminate' malaria (http://wyss.harvard.edu/staticfiles/newsroom/pressreleases/Gene%20drives%20FAQ%20FINAL.pdf) to envision how this might transpire in actual practice. How long will it take to see an impact, how much effort will be required to achieve any measurable success and how much of the Earth do you propose to treat? Will you be able to explain setbacks? Will you educate the public that there are several forms of malaria and several vector species? Scientists are obliged to explain situations fully and no group should be more cognizant of the immense challenges involved in actually carrying out a promise to eliminate malaria. Possibly the claims today represent unbounded enthusiasm over the huge potential of gene drives. Then I ask those issuing promises to bear in mind the battle against malaria will take place under uncontrolled and uncontrollable conditions with sometimes uncooperative weather, logistical complications and just plain unforeseeable issues. We live in a world in which workers vaccinating children against polio have been assassinated. It can be a tough place to conduct field trials, too.

*What goal(s) will gene drives enable us to reach?*

The entire world shares the common desire to eradicate infectious diseases. There may be several ways to achieve the diverse goals this will entail, how might gene drive technology fit productively in the larger effort? Many discussing gene drives appear to harbor the tacit opinion that this technology must be used and will substantially outperform all other approaches. The issues need to be considered thoughtfully and approached carefully due to a substantial risk for sparking an unproductive polarized debate between gene editing proponents and equally fervent opponents. Perhaps with care and due respect it will be possible set aside parochial interests and work toward common goals of disease eradication in the way(s) that make the most sense.

*What plans are being developed to communicate with the general public and environmental groups?*

Involving as they do plans to modify natural ecosystems, work with gene drives will ultimately face public scrutiny and comment. Scientists must be willing to do more than communicate amongst themselves in specialized journals and I urge my colleagues to take proactive steps to develop working associations with environmental organizations as soon as possible.

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