Bioteknologirådet
The Norwegian Biotechnology Advisory Board

14th February 2017

Statement on gene drives

This document was originally written in Norwegian, and has been translated for dissemination purposes.

New technology, called gene drive, has the potential to solve several significant health and ecological problems. At the same time, gene drives could have significant impact on the environment.

Gene drives make it possible, for the first time, to spread genetic changes in large populations of wild plants and animals, and thus override nature's evolutionary constraints. Scientists are now working to develop gene drives to prevent the spread of malaria by eradicating mosquito species that carry the parasite, and to preserve endangered species, amongst other things. The technology challenges established principles for risk assessment and regulation, and raises difficult ethical questions.

With this statement, The Norwegian Biotechnology Advisory Board aims to be a driving force in the national and international debate on the use and regulation of gene drives.

1.0 Summary of recommendations:

The Norwegian Biotechnology Advisory Board believes it is urgently important to discuss the science, politics and societal consequences of the use of gene drives, both nationally and internationally. The Board urges Norwegian authorities to be proactive in the work towards establishing international regulations for gene drives.

The Norwegian Biotechnology Advisory Board believes the potential benefits of gene drives are large, but also recognize that there are significant risks associated with the use of the technology in nature. The Board holds forth that further research is required and should be encouraged. All research and development of gene drives should be conducted openly and stepwise, and any proposal for release in the wild should be discussed in public international forums where various stakeholders are heard in the decision-making process.

The Norwegian Biotechnology Advisory Board recommends a moratorium on the use of gene drives until international regulations for handling and risk assessment are in place. Such regulations should be developed by for example relevant UN bodies, ensuring broad international consensus.

A majority of ten out of fourteen board members recommend that field trials should still be allowed as part of research if the gene drive can be constrained (for example, on a remote island). A prerequisite is that such field trials are conducted according to guidelines developed by major

international bodies such as the UN or EU. This ensures a stepwise process and emphasizes the precautionary principle, but allows a degree of risk where the potential benefit is significant.

A minority of two board members believe that a moratorium should include all field trials until a regulatory framework with broad international consensus is in place. They argue that the potential harmful effects of the use of gene drives can be substantial.

Another minority of two board members argue that potential eradication of malaria - a disease that claims half a million lives each year - is a weighty ethical reason to facilitate research and development of gene drives as much as possible, including limited field experiments where gene drives can be constrained (for example, on a remote island). It is sufficient that this research is carried out within existing national and international frameworks for GMO regulation and guidelines for research.

A joint Board recommends that research and development of self-regulating gene drives that only work over a few generations and other alternative methods of prevention and treatment of malaria and other proposed uses of gene drives, which are easier to control, should also be conducted.

2.0 Background – the principle of gene drive technology

Genetic variation in a population is governed primarily by two principles: random mutation and natural selection. Different mechanisms, both external factors such as radiation and pollutants and normal processes in a cell can lead to the emergence of mutations in the genome. Most mutations have either no effect or have negative consequences for the organism, and will usually disappear from the population over time. On the other hand, if a mutation gives the organism a competitive advantage, it is likely to increase in frequency in the population over time, since offspring who inherit it will have a survival advantage and get more viable offspring than those who do not. This is called natural selection.

How quickly a trait spreads in a population is, however, limited by the fact that an organism only contributes half of the genetic material to their offspring - so-called Mendelian inheritance (Figure 1 - top). Having two different genetic parents contribute to genetic diversity in a population.

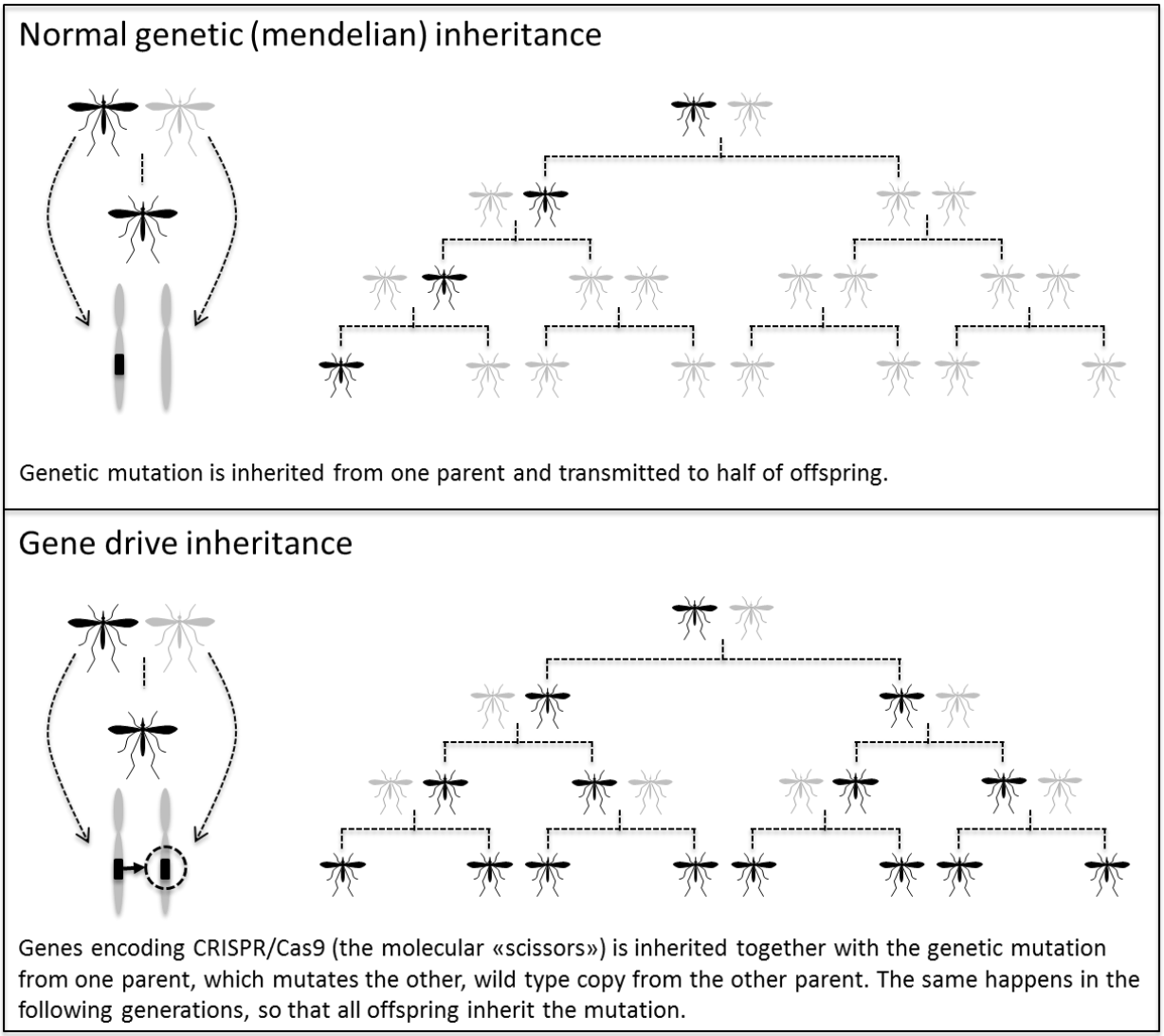
Gen drives can override the normal laws of inheritance, because they increase the probability that a gene variant is passed from parent to offspring to over 50%. This way, mutations that do not provide any competitive advantage to the organism can still spread in a population, and much faster than under normal conditions.

Certain naturally occurring gene drives do exist. An example is transposons, or "jumping genes", which can be copied and move to different places in the genome, thus increasing the likelihood that they are inherited. The idea of utilizing natural gene drives to spread genetic variants in a population was first launched over fifty years ago. However, it has proved technically difficult to create a working system using these mechanisms.

This changed with the development of the genome editing technology CRISPR in 2012. The method, a kind of molecular "scissors", makes it possible to create targeted changes in the genome of any type of cell in any living organism. A gene drive is made by inserting the “scissor” into the genetic material along with the desired gene mutation, as the "scissors" also cut the corresponding gene on the chromosome inherited from the other parent. Thus, all versions of the gene is mutated, and all offspring in the next generation will inherit it. And so the chain reaction continues: the genome

editing system (CRISPR) is inherited along with the desired gene variant, converts the corresponding gene on the second chromosome, and is passed on to all offspring in the next generation (Figure 1 - bottom). This implies that both the principles of genetic variation in a population is overridden; mutations can be targeted and are therefore not random, and natural selection is no longer a decisive factor for whether a trait manifests itself in the population. Gene drives based on genome editing therefore, for the first time, make it possible to modify genes in wild populations.

Figure 1: The principle of gene drive



In 2015, four proof-of-concept studies were published that showed that CRISPR-based gene drives work in principle in the laboratory: one in yeast[1], one in fruit flies[2] and two in mosquitoes.[3,4] In particular the last two received a lot of attention, since these studies aimed to develop methods to combat malaria.

If a sufficient number of organisms containing a gene drive are released in the wild, the gene drive could spread to an entire population. However, CRISPR-based gene drives only work in organisms that reproduce sexually. This excludes microorganisms such as bacteria and viruses, but include most plants and animals. There must not exist insuperable barriers to reproduction (e.g. geographical barriers), and the target organism should have a relatively short generation time and population structure that facilitates the spread of the gene drive. For example, it is estimated that it will take about 11 generations, or about one year, for a gene drive to spread to an entire population of malaria mosquitoes.[5] In elephants, however, it will take several centuries, since the generation time is 25 years, and there is a lower level of gene flow between subpopulations. The success rate will also depend on the target organism not developing resistance to the gene drive.

3.0 Examples of suggested use of gene drives:

3.1 Disease prevention using modified mosquitoes

Mosquitoes carry of a number of serious diseases, such as malaria, dengue fever, yellow fever and Zika. Malaria, in particular, is one of the biggest global health problems. In 2015, over 200 million people were infected, and about 500,000 died, mostly children under five.[6] The disease is caused by the parasite *Plasmodium*. Its main vector is the mosquito *Anopheles gambiae*, but malaria can also be spread by other *Anopheles* subspecies. So far, combating malaria using other means such as removal of breeding sites, insecticides, medicines and vaccines have had limited success. All of these approaches require infrastructure and organization, such as access to health care, and it can be difficult to reach all areas at risk. In addition, significant populations of A. gambiae have developed insecticide resistance.

Scientists now aim to create gene drives that can prevent the spread of malaria. It is not feasible to use the system in the parasite itself, since the rate of gene flow within the population is too low (reproduction often takes place within a single infected person). Mosquitoes carrying the malaria parasite are however very mobile, and can therefore effectively disperse gene drives within a population. Efforts are underway to create both mosquitoes that are resistant to the parasite, and mosquitoes only producing sterile females leading to eradication of the population over time. It is the second strategy that is believed to be the most effective, since parasitic resistance is difficult to maintain over time.

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[1] Di Carlo et al (2015) Safeguarding CRISPR-Cas9 gene drives in yeast. Nature Biotechnology 33.

[2] Gantz and Bier (2015) Genome editing. The mutagenic chain reaction: A method for converting heterozygous to homozygous mutations. Science 348.

[3] Gantz et al (2015) Highly efficient Cas9-mediated gene drive for population modification of the malaria vector mosquito Anopheles stephensi. PNAS 112.

[4] Hammond et al (2016) A CRISPR-Cas9 gene drive system targeting female reproduction in the malaria mosquito vector Anopheles gambiae. Nature Biotechnology 34.

[5] https://www.technologyreview.com/s/601213/the-extinction-invention/

[6] http://www.who.int/malaria/media/world-malaria-report-2015/en/

Other researchers are working to develop gene drives for species of *Aedes* mosquitoes, particularly *Aedes aegypti*, which is the main vector for the spread of dengue fever, yellow fever and Zika.

3.2 Fighting disease with Schistosoma

Schistosomiasis is a disease caused by parasites called flukes, and is a significant public health problem in tropical and sub-tropical areas. [7] The disease infects hundreds of millions of people annually. Scientists in the US have now initiated projects to develop gene drives to eradicate these flukes. [8] In this case, the parasite itself is the target organism, since it has a biology and population structure suitable for dispersal of a gene drive.

3.3 Eradicate pests to preserve other species

Estimates indicate that around 40 percent of the world's endangered species are island inhabitants. [9] One of the problems is invasive rodents (mice and rats) that are introduced with the shipping trade. A number of efforts have been initiated to eradicate the rodents from islands, primarily by the use of rodenticides. [10] The effectiveness of this strategy is limited, however, since it is not possible to use large amounts of poison in densely populated areas. In addition, the poison also harms non-target species.

Both researchers and the organization Island Conservation have stated that they would like to develop gene drives to eradicate mice and rats from the islands . [11,12] Most probably this will be gene drives that enable gender skewing, for example only allowing viability in male offspring, and therefore the eradication of the population over time.

Other specific suggestions include eradication of the mosquito species *Culex quinquefasciatus* from Hawaii that spreads bird malaria to endangered bird species, and eradication of amphibians in Australia that is damaging the native biodiversity. [13]

3.4 Spread favorable genetic variants for conservation purposes

Some have suggested using gene drives directly in endangered species to make them more genetically robust. For example, the Tasmanian devil (marsupial) now endangered due to an epidemic of face cancer. Recently a few individuals in the population were identified that are naturally resistant to the face cancer, and using gene drives to spread this gene variant to the other individuals has been proposed.[14]

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[7] https://sml.snl.no/schistosomiasis

[8] Personal correspondence with Dr. Kevin Esvelt, group leader, Massachusetts Institute of Technology (MIT), USA.

[9] Tershy et al (2015) The importance of islands for the protection of biological and linguistic diversity. Bioscience 65.

[10] Witmer et al (2007) The use of rodenticides for conservation efforts.
http://digitalcommons.unl.edu/cgi/viewcontent.cgi?article=1776&context=icwdm_usdanwrc

[11] https://www.wired.com/2016/06/save-galapagos-gmo-rats-go-wrong/

[12] https://www.scientificamerican.com/article/harnessing-the-power-of-gene-drives-to-save-wildlife/

[13] http://www.sculptingevolution.org/genedrives/safeguards

[14] https://www.wired.com/2016/08/genes-might-helping-tasmanian-devil-fight-off-face-cancer/

3.5 Agriculture

There are many potential applications for gene drives in agriculture. One suggestion is to use them to reverse pesticide resistance in weeds and insects,[15] or using gene drives to eradicate them.[16] Another suggestion is to spread desired traits in crops much faster than can be achieved by traditional means.

4.0 Consequences for the environment

Gene drive technology is developing fast, but no studies of how gene drives will affect ecology, population dynamics and evolution exist so far. There are many complex factors that will affect the outcome, which will vary depending on the species, the genetic trait that is changed, geography and interactions in the ecosystem, to name a few. For example, one could assume that a gene drive would have major consequences for the environment if used on a native species with key roles in an ecosystem, while it could have less impact if used on an invasive species that is not native to where it is released. The outcome of releasing a gene drive will also depend on the geographical distribution of the species and its sub-populations. If a population is geographically isolated, gene flow and thus the effect of a gene drive could be limited. Other relevant factors include whether other species will fill the empty ecological niche, and whether this will lead to positive or negative consequences for health and environment.

A significant concern is whether a gene drive can spread to other non-target species. This can theoretically happen if inter-species reproduction can occur, such as hybridization of closely related plant species. Another theoretical possibility is that a gene drive can be transmitted through horizontal gene transfer. We know for example that bacterial DNA can be inserted into the genomes of plants.[17] It has also been shown that horizontal gene transfer has taken place in other organisms such as animals and insects.[18] However, such events are infrequent, and mostly limited to certain specific genetic elements.

The consequences of releasing a gene drive will vary from case to case. If we take the eradication of *Aedes aegypti* as an example, the consequences of eradicating it in the Americas may not be so serious since the species is not native to that area (it was introduced with the slave trade around the 1500s), and primarily located in urban, densely populated areas. In contrast, eradication of *A. aegypti* from Africa, where it originated, could potentially have a bigger impact, since it is more likely to be integrated in the local ecosystem[19]. The effectiveness of the strategy to limit the spread of disease would depend on whether the niche is filled by other species of mosquito that can carry the infectious agent. Another question is whether one can succeeded in developing control systems to prevent the spread of the gene drive from America to Africa (discussed below).

Eradication of organisms as a means to combat disease is not a new phenomenon, and we have historical examples of successful strategies. Humans have for example largely succeeded in eradicating fleas and lice from many communities, and it is believed that this is one of the main

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[15] http://wyss.harvard.edu/staticfiles/newsroom/pressreleases/Gene%20drives%20FAQ%20FINAL.pdf

[16] National Academy of Sciences: Gene drives on the Horizon (2016) – report. https://www.nap.edu/read/23405/chapter/1

[17] Yue et al (2012) Widespread impact of horizontal gene transfer on plant colonization of land. Nature Communications 3.

[18] Hotopp (2011) Horizontal gene transfer between bacteria and animals. Trends in Genetics 27.

[19] Personal correspondence with William Ryan Easterday, researcher at The Centre for Ecological and Evolutionary Synthesis (CEES), University of Oslo.

reasons that plague disappeared from Europe.[19] In the 1950s, a program was initiated in the United States to combat screw worm flies (Cochliomyia hominivorax), that caused major losses to the livestock industry, by releasing sterile males. The result is that the screw worm fly is now extinct from the southern parts of the United States, as well as large parts of Mexico, Central America and Jamaica.[20] There is no evidence of any significant negative effects on the environment as a result of this action. A similar strategy is currently also used to reduce the population of *A. aegypti* to combat dengue fever, in which sterile male mosquitoes that produce non-viable offspring are released into nature. The difference is that sterility is achieved by genetic modification (without gene drive). According to the manufacturer Oxitec, this has led to a decrease in *A. aegypti* populations in release areas by around 90%, and local governments in Brazil have published data showing that the incidence of dengue fever in the release area Piracicaba has decreased accordingly.[21] Some have expressed concern that the reduction in the population of *A. aegypti* will cause the niche to be filled by the closely related species *A. albopictus*, which can also carry disease virus. So far, however, there is no evidence that it has happened.

Some believe it will be better to use a gene drive to modify a population, for example by making mosquitoes resistant to the malaria parasite, than to eradicate it, because the ecological consequences may be less severe. However, researchers state that there may be good reasons for choosing the eradication strategy. Firstly, it will probably be more effective (it is likely that the malaria parasite will become resistant to a resistance gene drive). Secondly, the gene drive will disappear when mosquitoes are eradicated, and not remain in nature as a risk factor like a resistance gene drive.

Other examples show that eradication of species can have negative consequences. For example, oyster overfishing has led to algal blooms and thus oxygen depletion and lower biodiversity along the US coast.[22] Another example comes from Sarigan Island in the Pacific, where the removal of goats and pigs to preserve forests and the local fauna led to overgrowth of an invasive vine plant.[23]

In complex ecosystems, the consequences of releasing a gene drive could be both so-called known unknowns (expected or foreseeable) and unknown unknowns (unexpected or unforeseeable).

5.0 Risk assessment

A central question is whether it is possible to pre-assess the risk of releasing a gene drive. The knowledge base in terms of gene drives is currently limited to four lab-based proof-of-concept studies. The risks will be different for the various applications, and each case must be considered separately. If gene drives are to be released in the wild, it is necessary to have suitable and sufficient risk assessment methods in place based on international consensus.

According to researchers at the Centre for Ecological and Evolutionary Synthesis (CEES) at the University of Oslo, it will be difficult to use hypothesis-driven modelling of effects of gene drives,

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[20] http://www.fao.org/docrep/U4220T/u4220T0a.htm

[21] http://www.oxitec.com/dengue-fever-cases-drop-91-percent-neighbourhood-piracicaba-brazil-oxitecs-friendly-aedes-released/

[22] Jackson et al. (2001) Historical overfishing and the recent collapse of coastal ecosystems. Science. 293(5530): 629-638. 2001.

[23] Kessler, C.C. 2002. Eradication of feral goats and pigs and consequences for other biota on Sarigan Island, Commonwealth of the Northern Mariana Islands. In: Veitch, C. R. and Clout, M. N. (eds.). Turning the tide: the eradication of invasive species, pp. 132-140. IUCN SSC Invasive Species Specialist Group, IUCN, Gland, Switzerland and Cambridge, UK.

since we know too little about the different parameters that determine the outcome. They therefore believe that such modelling cannot be used in risk assessment in a meaningful way.[24] A comprehensive report from the National Academy of Sciences (NAS)[Feil! Bokmerke er ikke definert.] in the US has tried to outline what guidelines for a risk assessment model should look like. Specifically, it addresses the concept of "ecological risk assessment", as used by the US Environmental Protection Agency (EPA), to evaluate the ecological impact (both positive and negative) of exposure to various stress factors, such as how pesticides affect the environment or endangered species. The aim of this model is to provide quantitative measures, with a long-term perspective and a framework for handling a large degree of uncertainty. Specifically, this involves extensive gathering of information during the initial phases of the process, followed by analysis and characterization of risks. In addition, the model can identify knowledge gaps and what data is needed to be able to provide meaningful answers. NAS believes such an approach could be used for risk assessment of gene drives, but that we need more research, both in the laboratory and in field trials, to be able to assess possible unintended effects, and how gene drives behave in different environments.

Some are worried that gene drives can spread unintended genetic elements if they insert at off-target sites in the genome. This is unlikely, however, since the gene drive is only able to cut the gene within which it is located, which is the target sequence. It is more likely that mutations could arise that would make the organism resistant to the gene drive or make the gene drive inactive.[25] To examine the effectiveness and safety of gene drives, studies are underway to determine empirically whether such effects are likely and to what extent. For example, the nematode worm *Caenorhabditis brenneri*, a model organism with a short generation cycle that can be grown in large numbers, is being used to investigate the prevalence of accidental mutations, chromosomal instability, the probability of spread of a gene drive to closely related species and other relevant factors.[8] In addition, one of the research groups that develop gene drives for malaria mosquitoes have built large, closed cages with artificial ecosystems where gene drives can be tested.[26]

6.0 Control mechanisms

Because gene drives are designed to spread throughout large populations, and because the consequences of releasing gene drives in the wild may be substantial and unpredictable, field trials are inherently risky. Efforts are therefore underway to develop control mechanisms to limit the spread of gene drives. One suggestion is to have a second gene drive that can reverse the first at hand, which can be deployed immediately if needed. This concept has been shown to work in yeast cells in the laboratory.[Feil! Bokmerke er ikke definert.] However, it is highly uncertain whether this will be sufficient to counteract the effects of the original gene drive in the wild. Another proposed system is called daisy-drive, where the gene drive stops working after a certain number of generations because it is designed to lose important elements each time it is copied.[27] The duration of the time it is functional and hence the extent of the spread in a population depends on it is constructed, and can be adjusted. This could be used as a strategy to limit gene drives to small populations. According to

[24] Personal communication with Prof. Nils Christian Stenseth, Centre for Ecological and Evolutionary Synthesis (CEES), University of Oslo.

[25] http://www.nature.com/news/gene-drives-thwarted-by-emergence-of-resistant-organisms-1.21397?WT.mc_id=FBK_NatureNews

[26] Personal communication with Professor Andrea Crisanti, Imperial College London, UK.

[27] Noble et al (2016) Daisy-chain gene drives for the alteration of local populations. BioRxiv. http://biorxiv.org/content/early/2016/06/06/057307

the lead researcher developing the daisy-drive system, they have now tested and verified that the simplest version is functional in yeast. Going forward, they also plan to test more advanced versions with more elements.[8] A third suggestion is to preserve the samples of the original species to be modified, so that they can be released again if something goes wrong.

The World Health Organization (WHO) believes there is great potential for the use of GM mosquitoes to fight diseases. They have drafted guidelines for laboratory research and field trials of GM mosquitoes, including gene drives.[28] They stipulate that initial research should be conducted in strictly controlled closed facilities and that any field trials should be carried out in geographically isolated areas. Gene drive release in the wild requires continuous monitoring of efficacy and both intended and unintended effects over time.

The US Defence Advanced Research Projects Agency (DARPA) under the Pentagon has initiated a program to develop methods to stop, remove or reverse unwanted genetic changes, whether the changes are caused by gene drives or other forms of genome editing.[29] Such strategies will require significant research.

7.0 A real alternative?

Many programs for natural resource management and public health exist worldwide, and a variety of methods are used to achieve their objectives. Examples are the use of pesticides against disease-carrying organisms, vaccinating populations or animal populations, introduction of new species in local ecosystems to keep the population of other organisms suppressed, or measures to protect endangered species.

For example, in the 1940s Brazilian authorities and a number of other South American countries deployed a program to eradicate *A. aegypti* using the insecticide DDT to control the spread of dengue fever. By early 1960s, the species had been removed from large parts of the continent.[30] However, the mosquitoes later gradually returned to these areas, in part because the program lost political support and was scaled down. The mosquitoes having developed resistance to DDT was another contributing factor. There are also active programs today to control or eradicate *A. aegypti*, and efforts have been intensified with the increase in the incidence of Zika virus.

Another example is the effort to eradicate invasive rodents that destroy large parts of the fauna on tropical islands. For instance, the organization Island Conservation run active programs to distribute large amounts of rat poison, and has succeeded in removing invasive rodents from several islands.[31] This has led to an increase in the populations of endangered species.

None of these strategies are risk free. Both pesticides and rat poison can be harmful to health and the environment. In addition, the efficacy can be limited. For example, Island Conservation have stated that a gene drive that only allows males to be born may be a more effective and less risky way to eradicate rat populations than to cover islands in rat poison.[Feil! Bokmerke er ikke definert.] This will also be more in line with the principles of animal welfare, since it does not involve suffering for the

[28] http://apps.who.int/iris/bitstream/10665/127889/1/9789241507486_eng.pdf?ua=1

[29] http://www.darpa.mil/news-events/2016-09-07

[30] http://www.scielosp.org/scielo.php?script=sci_arttext&pid=S1020-49891997000100023

[31] http://www.islandconservation.org/

organisms. The question is how a cost/benefit-assessment of a gene drive compares to that of alternative strategies in each case.

8.0 Ethics

Gene drives could enable us to solve significant health and ecological problems. We could therefore have a moral obligation to develop the technology, which thus expresses a moral imperative. Conversely, several challenges raise questions about whether use of the technology can be justified, both scientifically, politically and ethically.

When decisions are to be made in situations where there is scientific reason to expect harm to health or the environment, but one lacks sufficient knowledge to estimate the likelihood and extent of damage, the precautionary principle is recognized as a guiding principle, including in the EU and in Norway.[32] Application of this principle requires technical expertise, but also social and ethical considerations. Whether one should release gene drives is thus largely a political question. However, precaution is not exhaustive of the ethical assessment. For some, it will be inherently problematic to use gene drives in the wild.

8.1 Overriding evolution

One of the arguments is that it may be unacceptable to override evolution and the natural conditions in such a direct and fundamental way as with gene drives. Although we have changed the genetic makeup of organisms using traditional breeding and processing, introducing gene drives is something radically new. While genetic engineering is used to modify specific genes in certain organisms, for instance in plants used in food production and industry, gene drives could change virtually all individuals in wild species, with those potentially far-reaching consequences it might entail.

The arguments against this is based on nature setting limits to human manipulation. Whether one emphasizes that we should not upend nature's fragile balance, that we have no control over the consequences, or that we are not able to take responsibility for the outcome of such extensive intervention, the core of the argument is that we must respect nature.

It is therefore unacceptable to deliberately make interventions that can have major impacts on ecosystems, because it is impossible for people to have control over and responsibility for an intervention and its consequences on such a level. Evolution often works slowly, with tiny changes in each generation, so that species that interact in the environment are given time to adapt to a change. With gene drives, however, we will be able to make changes very rapidly, without giving interacting species time to adapt. This way, one can upset a fundamental ecological balance.

From another perspective, it is argued that human activity, such as greenhouse gas emissions and deforestation, have had major consequences for both the environment and climate, and that the use of gene drives can reinforce such a negative development.

From a more pragmatic perspective, one can argue that it is better to use gene drives to phase a population out over time through lack of reproduction than to kill individuals directly, for example by using poison. Some believe gene drives can also be a useful tool to reverse some of the damage we have inflicted on our planet. A counter-argument may be that it is not appropriate to use technology

[32] http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=URISERV%3Al32042

to fix a problem intitially generated by technology, for example by using gene drives to reverse pesticide resistance in weeds. What is needed is an approach that does not harm nature, rather than repairing human inflicted damage through actions that may lead to additional damage.

8.2 Do we have the right to eradicate species?

Gene drives also raise a well-known issue: technology to eradicate a species.

Within eco-centric environmental ethics, it is argued that species have intrinsic value regardless of whether they benefit humans or not, and that it is therefore fundamentally unethical to eradicate them.[33] In contrast, it has also been claimed that species do not have such unconditional value, since eradication of organisms such as pathogenic bacteria and viruses is viewed as positive.

Another argument assumes that there is an important distinction between life forms that have consciousness and the ability to feel pain and/or desire, and those that do not.[34] This argument implies, as argued by philosopher Peter Singer and others, that simpler life forms such as plants and insects do not have moral status, while the higher animals and humans do. The problem with this approach is that we do not have sufficient knowledge about the mental state of various organisms. Moreover, the well-established practice of eliminating organisms such as insects and rodents using pesticides and poisons implies that it is not immediately convincing to ascribe moral status at the level of the individual organism for some species, regardless of whether they are conscious and can feel pain. The question is whether we still can ascribe moral value to species where individuals do not have it. These are key issues in environmental ethics, and have implications for the assessment of gene drives that aim to eradicate species. Yet, they are not exclusive to gene drives, since we already use other means to achieve the same goal.

8.3 Environmental ethical perspectives

Gene drives, perhaps more than any other technology, presents us with the challenge of how to weigh benefit to humans against the risk to nature (and thus possibly to ourselves and our descendants), since its use can have major consequences for both. This conflict is reflected in two opposing environmental ethical approaches: Is nature primarily a resource that we are free to use for our own purposes within reasonable limits, or do we have moral obligations to refrain from making irreversible changes in nature as much as possible - because it has intrinsic value and / or to protect the interests of future generations. What weighs heaviest where one of the considerations must give way?

Ensuring and promoting sustainable development is a key principle in environmental ethics. One question is whether the aim is the well being of our descendants, or to limit the human environmental footprint. This is an important question where gene drives are used for public health purposes, such as prevention of malaria. In the case where a gene drive is used for conservation purposes, such as to preserve endangered species, the issue is more complex, since the purpose is preservation of nature rather than immediate human gain. Just as the risks and benefits of gene

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[33] Se for eksempel Rolston, H. III. *Philosophy Gone Wild: Essays in Environmental Ethics*. Amherst, NY: Prometheus, 1986

[34] Pugh. J (2016) Driven to extinction? The ethics of eradicating mosquitoes with gene-drive technologies. *Journal of Medical Ethics 42*.

drives will vary between cases, it is therefore also difficult to generalize about the ethical aspects of the technology.

8.4 Who will benefit?

The arguments against gene drives must be weighed against the arguments in their favour. We can, for example, have a strong moral imperative to save potentially many lives, as opposed to ensuring the further existence of the malaria mosquito. Malaria still claims the lives of around half a million people each year, despite many attempted measures such as use of mosquito nets, insecticides and the development of vaccines.**Feil! Bokmerke er ikke definert.** The consequences of not adopting a technology that can potentially reduce the incidence of the disease significantly can therefore be severe. Conversely, funds granted to developing gene drives could benefit other people if they are used in alternative ways.

Such difficult risk/benefit-assessments are highlighted in a report published by an Ad Hoc Technical Expert Group on Synthetic Biology appointed by the UN Convention on Biological Diversity (CBD) in 2015. The group emphasized that gene drives can be a tool to improve sustainable use of biodiversity and public health, but can also have adverse consequences for ecosystems.[35]

Assessments are also made difficult when a gene drive only benefits a limited number of people or geographical area, while the risks are borne by many who do not have any direct benefit. For people in tropical and sub-tropical regions the benefit of preventing the spread of malaria could be considerable, and they may, with good reason, wish to use the technology. Others will however have limited or no gain, but must bear the risk of adverse ecological effects. In the case of malaria, there is a potential north/south-conflict since developing countries are expected to get the benefits, while the risk, in principle, is borne by all. In this case, the 'risk' is primarily the loss of biodiversity, which is rarely a personal threat. However, one can imagine gene drives where the risk is more specific and affects people who do not stand to gain from their use. Should we, from an ethical perspective, be willing to accept a presumably real but limited risk to benefit those who are exposed to life-threatening disease, and who in many cases are less privileged? Are interventions with potentially adverse consequences for the environment acceptable if they prevent a serious illness? On the other hand, it is not certain that communities in malaria-prone areas will want to use gene drives, even if there is international political will to do so.

8.5 Societal values and affected parties

An important aspect in the assessment of gene drives is the consideration of societal values. On the one hand, gene drives can become a significant means of combating disease and promoting environmental conservation. On the other hand, they could also pose a significant threat to the environment. It can be challenging to deal with opposing views and values, and to determine how these will be weighted in the decision-making process.

It will be important to include various stakeholders in the discussions on the use of gene drives. However, it may be difficult to define who these should be. Which groups are affected geographically, and is it necessary to be directly affected to be heard?

[35] https://www.cbd.int/doc/meetings/synbio/synbioahteg-2015-01/official/synbioahteg-2015-01-03-en.pdf

Decisions about whether to release gene drives, and thus whether to accept the risks involved, should be based on broad public dialogue.

8.6 Alternative approaches

Before the advent of gene drives, the lack of effective treatments for malaria was often cited as an example of the unfairness of medical research funding and how the industry did not prioritize diseases in developing countries with limited potential for profits. Even though the malaria research field has also received substantial investments in later years with limited therapeutic results, it is important not to forget that there may be alternative strategies.

For example, an alternative to eradicating the malaria mosquito could be to make the mosquitoes unable to carry the malaria parasite. This way, one can avoid eradication of an entire species "just" because it is the unfortunate vector. However, the continued presence of a gene drive in a population can increase the risk of adverse events. How different options are weighted and evaluated will vary from case to case.

9.0 Precautionary Principle – different approaches

The precautionary principle has been implemented in a number of regulatory frameworks, particularly those that concern the environment. It suggests that when an action can have serious negative consequences, and we have insufficient knowledge about these consequences or the probability that they will take place, we should prohibit the action until we know more about them. This can lead to various courses of action, such as prohibition, special requirements for field trials etc.

There are various interpretations of the precautionary principle:

- A weak version holds that where there are threats of serious or irreversible damage, lack of full scientific certainty shall not be used as a reason for postponing cost-effective measures to prevent environmental degradation. Such a formulation of the principle is found in the 1992 Rio Declaration on Environment and Development and the Convention on Climate Change.[36] This means that measures to limit the damage is assessed in a cost/benefit-perspective. The burden of proof is often placed on those who want to implement the restrictive measures.
- In moderate versions of the principle, the presence of a possible threat requires preventative steps to be taken, even where there is no scientific evidence that the damage will actually occur. There is normally no requirement that the measures should be weighted against the cost of implementing them. Here, the burden of proof can be placed either on those who want to apply the precautionary principle or those who propose an activity/technology. Such an interpretation of the precautionary principle is the basis of the EU-legislation.[37]
- Strong versions of the principle differ primarily from weak and moderate ones in that the burden of proof is entirely placed on those who propose an activity/technology, who must be able to prove that it does not pose an unacceptable risk. Such an approach also implies that one will not accept any such risks regardless of the benefit of the activity. An example of

[36] http://www.unep.org/documents.multilingual/default.asp?documentid=78&articleid=1163

[37] http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=URISERV%3Al32042

such an interpretation is found in the Earth Charter, an international declaration on sustainable development.[38]

The precautionary principle has been criticized for lack of clarity, and being challenging to operationalize. However, its broad formulation is also a strength, since it can be used in many contexts, including in environmental, climate and health policies, and allows different a case-by-case assessment. How one interprets the precautionary principle will be of great importance for assessing, managing and regulating gene drives. Use of gene drives will by its very nature involve a certain degree of risk and uncertainty, also at the research stage. A strict interpretation of the precautionary principle can make it difficult do the required research to obtain sufficient information to risk assess a gene drive, such as field trials.

10.0 Transparency in research

Research groups that develop gene drives have actively advocated for transparency and openness. For instance, they want no field trials or other release to happen without the political decision being rooted in broad public debate. Moreover, they want any such plans to be published prior to development and implementation, and that all experimental data be published and preferably peer reviewed.[39] Dr. Kevin Esvelt, one of the inventors of the gene drive technology and patent applicant has stated that he will use the patent, if awarded, to ensure that researchers reveal their research plans before the are implemented, to commit to following specific safety procedures.[40]

11.0 Industry and patents

Gene drive technology involves potentially large economic gains, particularly in the agricultural sector and the pharmaceutical industry. However, there is general agreement that individual companies should not have sovereignty of such powerful technology where the adverse consequences could be significant. Thus, The Broad Institute, holder of one of the CRISPR patents, specifically prohibited the use of the method to develop gene drives in its licensing agreement with the agrichemical company Monsanto.[41] As previously mentioned, Dr. Esvelt wants to attach a number of conditions to the licence of the technology, including full transparency about development plans. Others have advocated that all rights related to the technology should be consigned to a neutral international body, for example under the UN, similar to nuclear technology.[42]

12.0 Misuse and accidental release

Some are worried that gene drives will be misused. An example is the use in warfare, for example by destroying the crops of a neighbouring country. Another example is in bioterror, for example by

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[38] http://earthcharter.org/

[39] https://www.technologyreview.com/s/601634/meet-the-moralist-policing-gene-drives-a-technology-that-messes-with-evolution/

[40] https://www.technologyreview.com/s/602633/stop-gene-spills-before-they-happen/

[41] https://www.statnews.com/2016/09/22/monsanto-licenses-crispr/

[42] https://www.theguardian.com/science/political-science/2016/jun/09/the-national-academies-gene-drive-study-has-ignored-important-and-obvious-issues

making mosquitoes or other vectors that feed on humans more likely to spread disease, or by endowing them with genes that produce toxins. There is also a risk that some will be able to develop and release gene drives in good intention, but outside governmental control.

Dr. Esvelt believes gene drives are not particularly suitable as bioweapons. Firstly, the rate of spread is slow compared with pathogens such as viruses and bacteria. Secondly, they are easily detected by DNA sequencing, and can probably be neutralized with a reversal gene drive.[8]

Nevertheless, the technology is on the radar of a number of political bodies and defence organizations, including American intelligence and the UN. The Norwegian Defence Research Establishment (FFI) is also interested in acquiring knowledge on both genome editing in general, and gene drives in particular. One of the main reasons for concern is that the technology is relatively easy to master, and therefore in theory can be adopted by many.

Another point of concern is accidental release of gene drives from research laboratories. In theory, these could spread to wild populations, given that there are fertile organisms of the same species in the area. Esvelt believes it is highly unlikely that the accidental release of a gene drive leads to extinction of a species. For that to happen, the gene drive must be very carefully designed for that specific purpose, the circumstances must be very favorable for spreading, and the gene drive mustn't stop working by chance, for example by inactivating mutations or the gene drive organism dying before it reproduces. However, Esvelt believes that accidental spills will be very damaging to public confidence in technology, regardless of the consequences or lack thereof, and may delay its application to disease control for many years.[8]

13.0 Regulation

Gene drives involve the insertion of genetic material in an organism's DNA by genetic engineering, and will therefore indisputably be covered by existing GMO legislation, including the Norwegian Gene Technology Act. However, gene drives pose particular challenges, because in many instances a gene drive can cross borders and jurisdictions since they are designed to spread to large populations over vast geographical areas. Thus, an international regulatory framework is necessary.

The Cartagena Protocol, an international agreement under the UN Convention on Biological Diversity (CBD), regulates trade with genetically modified organisms, to protect biodiversity and health during transport, handling and use of genetically modified organisms. The precautionary principle must be applied, and the parties are obligated to develop a national legislative framework for GMO. The agreement regulates genetically modified mosquitoes through provisions concerning the release and transport of GMO. Provisions that a State may refuse the import of GMOs may, however, prove particularly difficult to enforce in practice when it comes to gene drives. Furthermore, not all nations have ratified the Cartagena Protocol, such as the US, where much of the research on gene drives is taking place.

There are also other international frameworks that may have implications for certain uses of gene drives, such as military use, e.g. the UN Convention (1977) on the Prohibition of Military or Any Other Hostile Use of Environmental Modification Techniques (ENMOD) and the UN Convention (1972) on the Prohibition of Biological Weapons (BWC).

However, none of the existing frameworks are ideal for regulating gene drives. The Nuffield Council on Bioethics in the UK proposes a flexible system where RRI (Responsible Research and Innovation) is central, and can be adapted to the technology case by case.[43]

There is also a need to clarify who is or should be responsible for any adverse consequences that may arise after the release of a gene drive.

These issues are expected to be discussed at several upcoming international forums, which may yield specific proposals for regulation of gene drives in the future. In addition to party meetings under the Convention on Biological Diversity, several international organisations under the UN-system can be relevant forums for discussions on international regulations for gene drives, such as UNEP, FAO and WHO.

14.0 Urgent need for international debate

The gene drive field is developing rapidly, and many are optimistic about the future use of the technology. For instance, the two aforementioned malaria projects have received significant support from both public and private funds. The Bill & Melinda Gates Foundation provided $ 75 million to researchers at Imperial College in London that are developing a gene drive to eradicate malaria mosquitoes, and hopes to have the technology ready by 2018, with subsequent approval of application in the wild by 2029[44]. An Indian fund called Tata Trust of Mumbai has given $ 70 million to researchers at the University of San Diego that are developing a gene drive to make malaria mosquitoes resistant to the parasite[45].

The National Academy of Sciences in the US, one of the world's most reputable scientific organizations, believes the evidence base is currently insufficient to support the release of gene drives, but that their potential in both basic and applied research is so significant that further research both in the laboratory and carefully controlled field trials is justified[Feil! Bokmerke er ikke definert.].

Others believe that gene drives involve so much uncertainty and unpredictable consequences for the ecosystems that their use cannot be justified. For instance, during its World Conservation Congress conference in 2016, the International Union for the Conservation of Nature (IUCN) proposed a moratorium, a self-imposed ban, on gene drive research until the issue has been carefully evaluated[46].

When the Parties to the CBD and the Cartagena Protocol met in December 2016, a proposal for a moratorium on all applied research and the use of gene drives was put forth by several environmental organizations. They believe no regulatory framework or risk assessment system is adequate, and furthermore highlight the inherent uncertainty and various ethical challenges that arise when using gene drives. In contrast, a number of researchers and academic institutions argued that such a moratorium would be irresponsible and highly detrimental to the development of this technology. They believe that any definitive decision on the use of gene drives are premature at best at this early stage of research, and that it would go against the principle of case-by-case evaluation.

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[43] The Nuffield Council on Bioethics. Genome editing: and ethical review (2016). http://nuffieldbioethics.org/project/genome-editing/ethical-review-published-september-2016/

[44] https://www.technologyreview.com/s/602304/bill-gates-doubles-his-bet-on-wiping-out-mosquitoes-with-gene-editing/

[45] http://www.sandiegouniontribune.com/news/science/sd-me-tata-gift-20161018-story.html

[46] https://portals.iucn.org/congress/motion/095

However, they want a continuous and open dialogue, in which the parties to the CBD also participate, to find the best framework for regulation, risk assessment and the use of gene drives.

The parties rejected the proposal for a moratorium, instead issuing a statement urging a precautionary approach when testing gene drives, in line with what the researchers themselves emphasize.[47,48] The subject will most likely be revisited at the next meeting of the Parties in 2018, and also at a number of other forums in the future.

The consequences of a moratorium will depend on its scope. In some cases, it may limit the unauthorized use of a technology, while stimulating research to gather information, build competence and establish appropriate regulatory frameworks. In other cases, a moratorium can result in less research being carried out, for example due to decreased funding.

Because gene drives do not respect geographical boundaries, because the consequences of releasing them could potentially be significant, because there is disagreement about whether they should be used and because the technology is developing rapidly, there is an urgent need for international debate. Any decision about the application of the technology requires international cooperation and grounding in a common framework. It will also be important to have societal consensus that the expected benefits outweigh the potential negative risks, and that we can accept an inevitable degree of uncertainty about the outcome.

15.0 The Norwegian Biotechnology Advisory Board recommendations:

The Norwegian Biotechnology Advisory Board believes it is urgently important to discuss the science, politics and societal consequences of the use of gene drives, both nationally and internationally. The Board urges Norwegian authorities to be proactive in the work towards establishing international regulations for gene drives.

Furthermore, The Norwegian Biotechnology Advisory Board believes the potential benefits of gene drives are vast, but also recognize that there are significant risks associated with the use of the technology in nature. The Board holds forth that further research is required and should be encouraged. Such research is also important in order to develop safeguards against gene drives with unintended consequences, that are released by accident or that are misused.

The Board also believes that all research and development of gene drives should be conducted openly and stepwise, and any proposal for release in the wild should be discussed in public international forums where various stakeholders are heard in the decision-making process.

The Norwegian Biotechnology Advisory Board recommends a moratorium on the use of gene drives until international regulations for handling and risk assessment are in place. The Board believes this is important because gene drives could spread across borders and there are limited opportunities for reversal. Such regulations should be developed by for example relevant UN bodies, ensuring broad international consensus.

The Board members Inge Lorange Backer, Cathrine Bjorvatn, Kristin Halvorsen, Gunnar Heiene, Arne Holst-Jensen, Torolf Holst-Larsen, Bjørn Myskja, Sonja Sjøli, Birgit Skarstein and Dag Inge Våge recommend that field trials should still be allowed as part of research if the gene drive can be

[47] https://www.cbd.int/doc/decisions/cop-13/cop-13-dec-17-en.pdf

[48] http://www.nature.com/news/gene-drive-moratorium-shot-down-at-un-biodiversity-meeting-1.21216

constrained (for example, on a remote island). These members believe that field trials are essential for understanding how gene drives work in complex ecosystems and to conduct a sufficiently informative risk assessment for full-scale release. They also believe that such field trials will be important to develop appropriate international regulations. A prerequisite is that such field trials are conducted according to guidelines developed by major international bodies such as the UN or EU. This ensures a stepwise process and emphasizes the precautionary principle, but allows a degree of risk where the potential benefit is significant.

The Board members Bjørn Hofmann and Benedicte Paus believe that a moratorium should include all field trials until a regulatory framework with broad international consensus is in place. They argue that the potential harmful effects of the use of gene drives can be substantial.

The Board members Petter Frost and Raino Malnes argue that potential eradication of malaria - a disease that takes half a million lives each year - is a weighty ethical reason to facilitate research and development of gene drives as much as possible, including limited field experiments where gene drives can be constrained (for example, on a remote island), if such research is necessary for adequate risk assessment. A moratorium on field testing will most likely slow research. Therefore, such a moratorium affecting research should not be introduced. It is sufficient that this research is carried out within existing national and international frameworks for GMO regulation and guidelines for research.

A joint Board recommends that research and development of self-regulating gene drives that only work over a few generations and other alternative methods of prevention and treatment of malaria and other proposed uses of gene drives, which are easier to control, should also be conducted.

(Sign.)

Kristin Halvorsen
Board leader

(Sign.)

Ole Johan Borge
Director

Case officer: Sigrid Bratlie, senior advisor