

FAQs: Gene drives

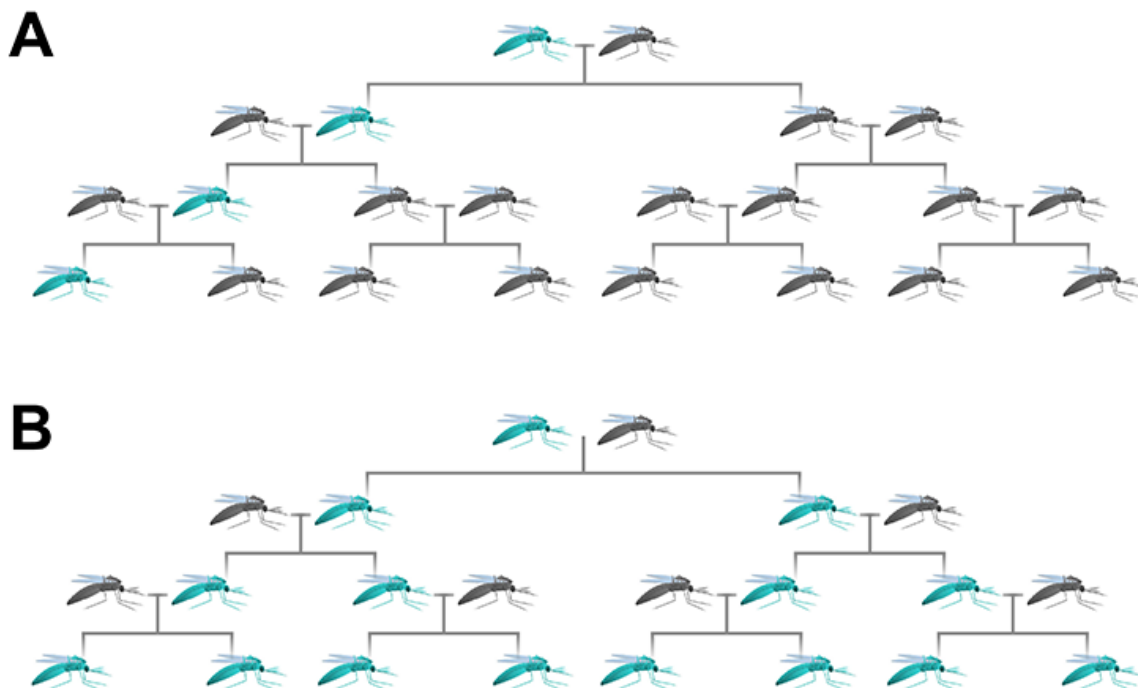
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What is a gene drive?

During normal sexual reproduction, each of the two versions of a given gene has a 50 percent chance of being inherited by a particular offspring (Fig 1A). Gene drives are genetic systems that circumvent these traditional rules: they greatly increase the odds that the drive will be passed on to offspring. This can allow them to spread to all members of a population (Fig 1B) even if they reduce the chance that each individual organism will reproduce.

One example in nature is a gene called the “P element,” which appears to have been absent before 1950 but is now found in nearly all fruit flies worldwide even though it doesn’t seem to confer any advantage to individual flies. Almost every sexually reproducing species has either an active gene drive or the broken remnants of one in its genome.

Figure 1



CAPTION: A) An organism carrying one copy of an altered gene (blue) normally passes it on to 50% of offspring. B) A gene drive can ensure that nearly all offspring inherit the altered gene, causing it to rapidly spread through the population - even if it is mildly deleterious to each individual’s chance of reproducing.

What are engineered gene drives?

Gene drives might be used to spread particular genetic alterations through targeted wild populations over many generations. Because they could alter the traits of entire populations of organisms, they represent a potentially powerful tool for the sustainable management of ecosystems. As with any emerging technology, the possibility of using engineered gene drives carries with it new concerns.

What might gene drives be able to do?

Gene drives might be used to:

- Eliminate diseases such as malaria, dengue, yellow fever, West Nile, sleeping sickness, Lyme, and others by altering insect species to no longer spread them
 - Malaria, which is carried by mosquitoes, kills more than a half million people every year, most of them children, and sickens 200 million more
- Eradicate invasive species
 - The top ten invasive species in the United States cause an estimated \$42 billion in damages every year
 - Many native species are driven extinct due to pressure from competing invaders
- Pave the way toward sustainable agriculture by reversing pesticide and herbicide resistance
 - For example, gene drives might make resistant weeds vulnerable to glyphosate, a widely used herbicide important for no-till agriculture
 - By 2012, glyphosate-resistant weeds had infested 25 million hectares of US cropland

Is this a new idea?

No, gene drives are well-documented in nature – and the idea of using gene drives as a potential way to control disease-carrying insect populations was first outlined in the 1940s. About ten years ago, Professor Austin Burt of Imperial College London first proposed a novel type of gene drive that relies on cutting DNA to alter populations in order to reduce the spread of disease.

What *is* new is that scientists now have the genetic tools that could let them alter almost any gene in any sexually reproducing species and spread those alterations through wild populations over generations – but only if the public agrees that the alteration is a good idea.

What technology might enable us to build gene drives to alter different species?

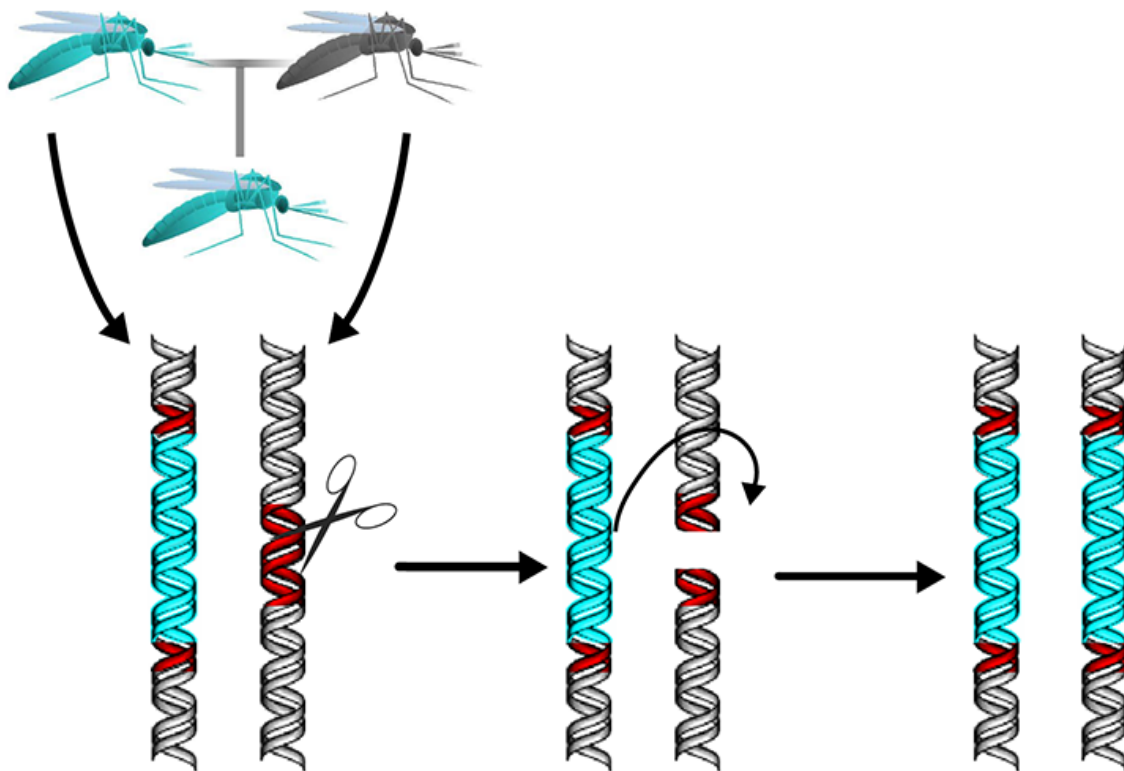
A powerful new genome editing tool called CRISPR/Cas9 Genome Editing, which was first introduced by scientists at the Wyss Institute and Harvard Medical School and the Broad Institute of Harvard and MIT, makes the idea of engineered gene drives feasible. The CRISPR system allows scientists to precisely insert, replace, delete, or regulate genes in many different species. The new advance describes related methods that may allow it to drive those alterations through sexual populations.

How does CRISPR work?

Scientists drew their inspiration for the CRISPR tool from a sophisticated form of bacterial self-defense. Bacteria use a system called CRISPR to store DNA from invading viruses so they can recognize and cleave that foreign DNA later when the invader returns. CRISPR-associated (Cas) enzymes do the cutting, and one in particular, an enzyme known as Cas9, can cut DNA at exactly the location dictated by a snippet of RNA. Scientists can program this RNA to seek out precise DNA sequences in the genome to be edited – and can also insert new specific gene sequences (Fig 2) – hence the highly efficient and specific targeting power of the CRISPR system.

Because CRISPR is so flexible and works in so many species, scientists will likely be able to drive almost any trait they know how to alter.

Figure 2



CAPTION: In organisms that inherit one drive-containing and one wild-type chromosome, the drive cuts the wild-type chromosome, causing the cell to copy the drive when it uses the drive-containing chromosome as a template to repair the damage. Because it now has two copies of the drive (and whatever alteration the drive is spreading), all of the organism's offspring will inherit a drive-containing chromosome to repeat the process.

Would engineered gene drives work in any species?

No, only in species that mainly reproduce sexually, such as insects, animals, and most plants. The time required to spread the alteration to most individuals in a population depends on the time between successive generations and how many drive-containing organisms are released. That means drives will work much faster in fast-reproducing species, especially if they can be reared and released in large numbers like insects.

Could gene drives affect human populations?

Not without taking centuries. As noted above, they take a long time to spread through populations with long generation times. For example, if we introduced a trait into elephants (which have a long generation time like humans) using a gene drive today, there would only be four times as many elephants with that trait in 100 years as if we didn't use a drive. That assumes no one decided to remove the trait in the meantime, which is quite possible.

What about crops?

It's possible but unlikely. Gene drives require efficient genetic mixing in a population in order to spread – and most crops today are grown from seed corn produced under controlled conditions. Similarly, cattle and most other domesticated animals are the products of tightly controlled breeding programs that rely heavily on artificial insemination.

Has anyone built an actual gene drive?

Not one that might spread through wild populations. Scientists have successfully built engineered gene drives that can only spread through transgenic laboratory populations of mosquitoes and fruit flies using earlier technologies. Because gene drives will impact shared ecosystems, the team behind this announcement felt it was their responsibility as scientists to start a public conversation well in advance of actually testing them.

What are some of the potential challenges of trying to engineer a gene drive?

First, the drive must be able to cut the target gene, which is easy with CRISPR. Second, it has to avoid harming the organism's ability to reproduce, as that will slow the rate at which it spreads through the population. For example, it needs to cut the target gene but nothing else. Third, it has to be accurately copied, which is a problem for drives based on other technologies but shouldn't be much of an issue for CRISPR. Fourth, it has to be evolutionarily stable – it can't accidentally make organisms that have a mutation preventing the drive from cutting and being copied. CRISPR can help with this by targeting multiple adjacent sites in important genes, so any organism with a mutation in one site will still be cut at the others and subsequently overwritten. Hardest of all, copying the drive isn't the only way the cell can repair the break – it can just jam the broken DNA ends together. Which pathway it uses depends on the species and developmental stage. The engineered gene drive that spreads through transgenic mosquitoes almost always uses the copying path without requiring any optimization. In contrast, the corresponding drive in fruit flies required a great deal of optimization and never reached the same

efficiency. Right now, we just don't know which organisms will be easy and which difficult. The team suggested several ways existing technologies might bias the pathway choice, but they have yet to be demonstrated in the laboratory.

What are the limitations of gene drives?

- They require many generations to spread through populations. The total time depends on the reproduction cycle of the organism, the number of drive-carrying individuals introduced into the population, the efficiency of the drive, gene flow dynamics and more.
 - For example, it might take a couple of years to alter an insect population. To put this in perspective, if you introduce a gene drive into only 10 of a constant population of 100,000 organisms, it would take about 16 generations for it to spread to 99% of the population under (unrealistically) optimal conditions. But existing programs release billions of radiation-sterilized insects at once to control pests, so drives could theoretically be spread much more quickly by releasing a lot of drive-containing organisms - at least for species that are easily reared.
- Gene drives can only reliably edit genes and sequences that are important for the organism's survival and reproduction. Sequences that aren't important can only be removed, not edited.
- They can't alter asexually reproducing populations such as bacteria and viruses and will have trouble with species that can reproduce with and without sex, like many plants.
- Some types of alterations would need to be continually reintroduced. For example, a driven trait that is somewhat harmful to the organism will eventually break. New drives would be needed to overwrite the broken versions with new and functional copies. Similarly, a drive that reversed herbicide resistance in a weed would have to fight against natural selection in areas where the herbicides was applied. Periodically introducing new drives would help.

What are some possible adverse effects of gene drives?

We are still learning how ecosystems work. It's possible that a particular altered trait could cause unexpected and possibly harmful side-effects on other organisms when spread through a particular species using a drive. The risks will primarily depend on the alteration and species rather than on the drive itself. This is why proposed gene drive must be evaluated on a case-by-case basis – it's all about the trait, species and ecosystem in question.

What are some possible safety measures that could be put in place?

- We can learn to build and optimize gene drives in a species without risking release into wild populations by separating required components (so they can't be copied together) and having them cut sequences that aren't present in wild populations.
- Drives that could theoretically spread through a wild population could be safely developed and tested in laboratories located in areas where the target species can't survive and find mates. For example, drives affecting tropical species could be developed and tested in temperate laboratories and vice versa.

- We could begin studying how the alteration might affect the ecosystem by releasing lots of organisms that have the alteration but not the drive, ideally in a contained setting. Scientists working with transgenic insects intended for release have developed a long list of such precautionary measures.
- Driven alterations can be reversed with another drive. The team recommends simultaneously building and testing a reversal drive for every primary drive that could spread a trait through a wild population. If something starts to go wrong, the reversal drive could be quickly released to undo the genomic changes. This wouldn't necessarily reverse all the ecological consequences, but it could prevent additional unwanted side-effects.
- Populations can be immunized against gene drives, so if we're concerned about a drive affecting a particular population, we could use another gene drive to immunize them against it.
- It should be possible to alter a distinct target species or subpopulation but not related non-target populations.

What are some of the key barriers that remain?

Gene drives are still an emerging technology. Getting them to work well in a new species could take many years, or it could work on the first attempt. It will depend on the species and we probably won't know until we try.

Since the effects of gene drives will primarily depend on the type of alteration and the species, not on the drive itself, each proposed alteration must be evaluated on a case-by-case basis.

Considerable research will be needed to better understand how individuals, populations and ecosystems will respond to each proposed alteration.

The release of gene drives in the United States will require approval by the Food & Drug Administration (FDA) for animals and one of several agencies for plants and insects. Current and relevant domestic and international policies are not adequate, and the authors call for a new approach to defining regulations. This is another reason the team is calling for a public conversation well in advance of candidate gene drives being tested in the wild.