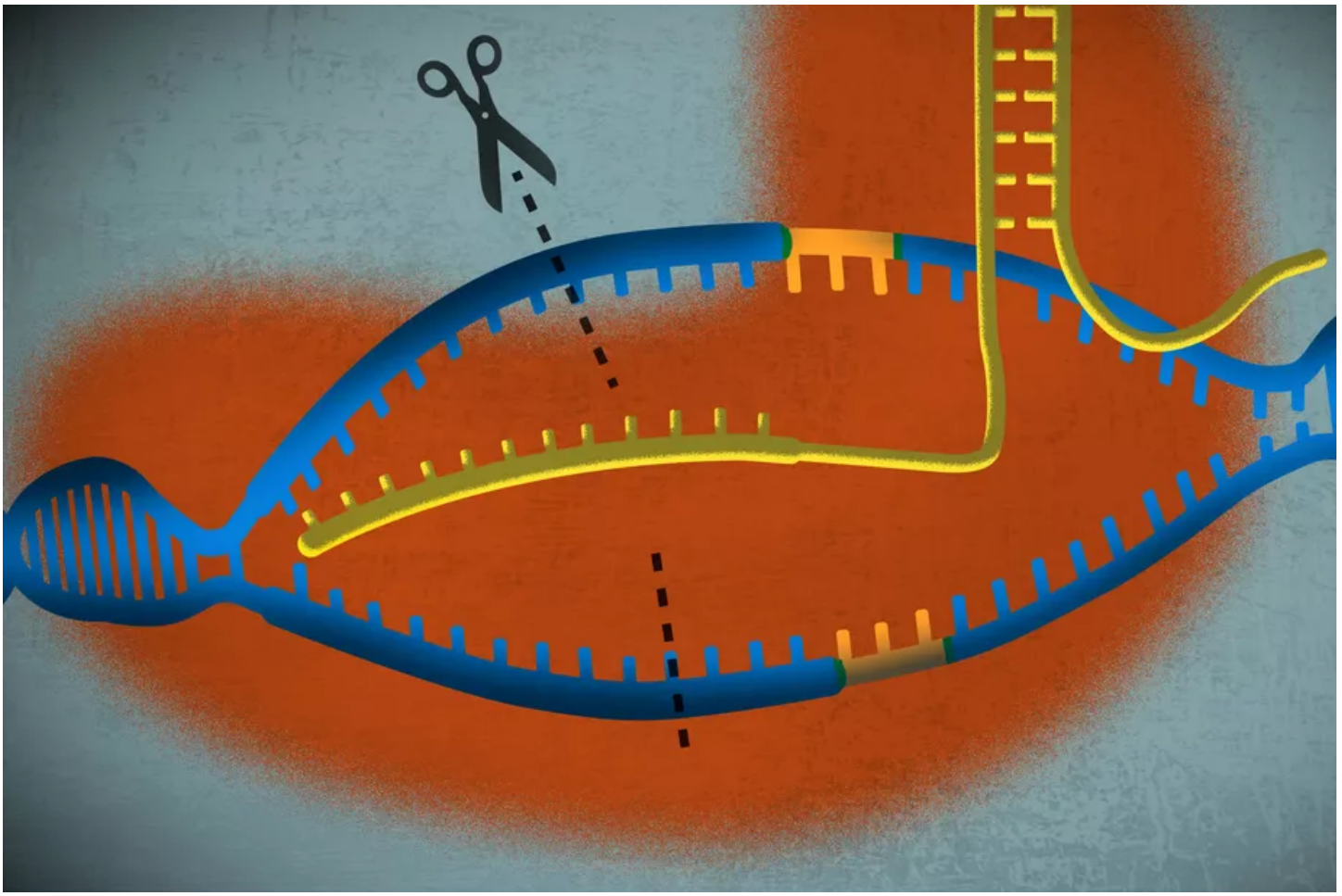
A simple guide to CRISPR, one of the biggest science stories of 2016

Updated by Brad Plumer and Javier Zarracina | *Dec 30, 2016, 3:32pm EST*



The scissors are, of course, metaphorical. | Javier Zarracina

One of the biggest and most important science stories of 2016 will probably *also* be one of the biggest science stories of the next decade. So this is as good a time as any to get acquainted with the powerful new gene-editing technology known as CRISPR.

If you haven't heard of **CRISPR** yet, the short explanation goes like this: In the past four years, scientists have figured out how to exploit a quirk in the immune systems of bacteria to edit genes in other organisms — plant genes, mouse genes, even human

genes. With CRISPR, they can now make these edits quickly and cheaply, in days rather than weeks or months. (The technology is often known as CRISPR/Cas9, but we'll stick with CRISPR, pronounced "crisper.")

Let that sink in. We're talking about a powerful new tool to control what genes get expressed in plants, animals, and even humans. The ability to delete undesirable traits and, potentially, add desirable traits with more precision than ever before.

In 2016 alone, researchers have shown CRISPR can do some truly astounding things, like create **mushrooms that don't brown easily** or edit bone marrow cells in mice to **treat sickle-cell anemia**. Down the road, CRISPR might help us develop drought-tolerant crops, create powerful new antibiotics, or treat diseases like cystic fibrosis. CRISPR might one day even allow us to **wipe out entire populations of malaria-spreading mosquitoes** or **resurrect once-extinct species** like the passenger pigeon. And, while there are real limits to what CRISPR can do, researchers are working to overcome them.

Much of the hype around CRISPR has focused on whether we might **engineer humans with specific genetic traits** (like heightened intelligence), particularly after Chinese researchers showed **they could edit human embryos** this year. But in some ways, that's a sideshow. "Designer babies" are still far off, and there are enormous obstacles to making those sorts of complex genetic modifications. The stuff that's closer at hand — from new therapies to revolutions in our understanding of the genome — is what's most exciting. So here's a basic guide to what CRISPR is and what it can do.

What the heck is CRISPR, anyway?

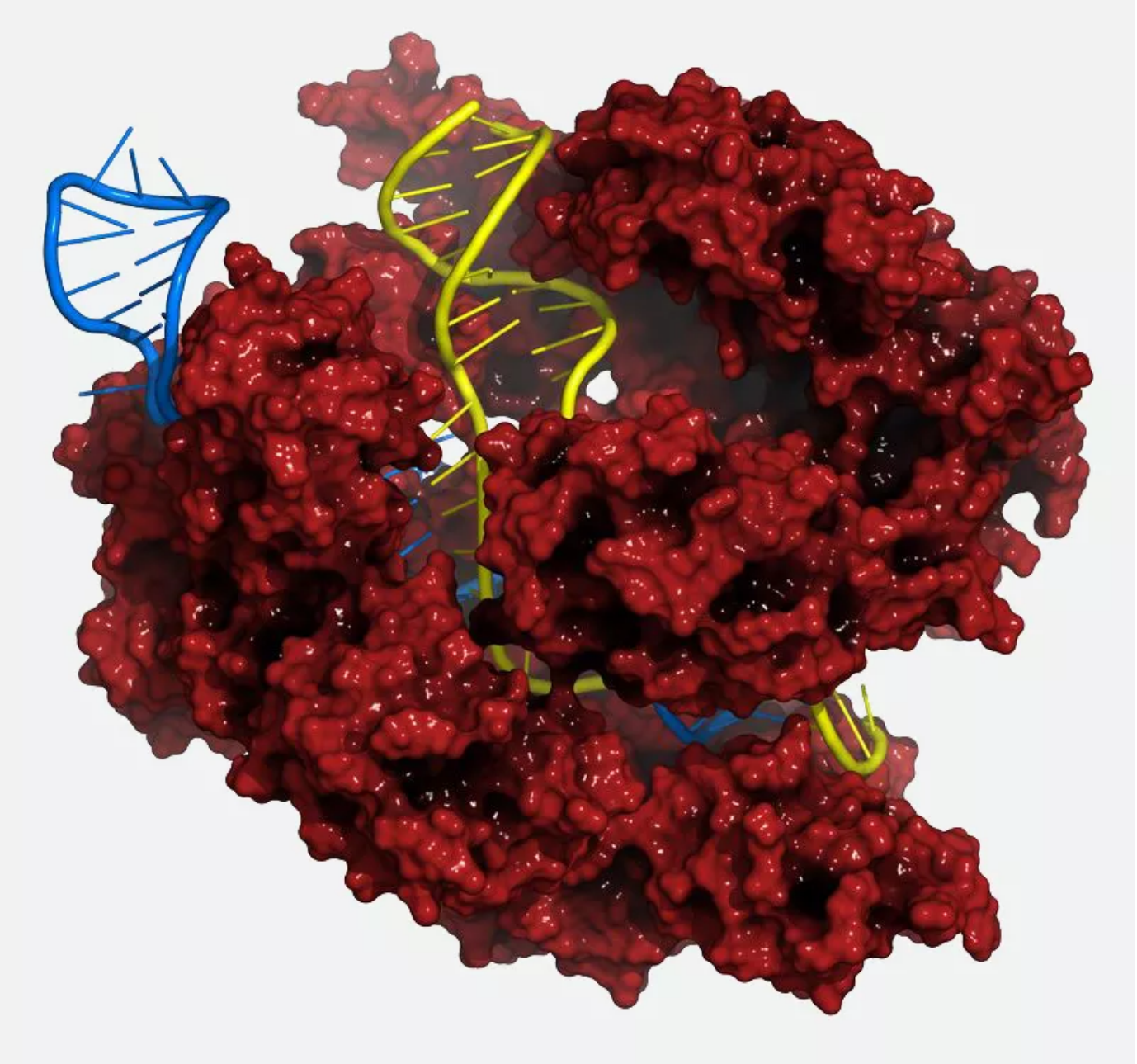
Genome Editing with CRISPR-Cas9

If we want to understand CRISPR, we should go back to 1987, when Japanese scientists studying *E. coli* first came across some unusual repeating sequences in the bacteria's DNA. "The biological significance of these sequences," **they wrote**, "is unknown." Over time, other researchers **found similar clusters** in the DNA of other bacteria (and **archaea**). They gave these sequences a name: Clustered Regularly Interspaced Short Palindromic Repeats — or CRISPR.

Yet these CRISPR sequences were mostly a mystery until 2007, when food scientists studying the *Streptococcus* bacteria used to make yogurt **showed** how these odd clusters actually served a vital function: They're part of the bacteria's immune system.

See, bacteria are under constant assault from **viruses** and produce enzymes to fight off viral infections. Whenever the bacteria's enzymes manage to kill off an invading virus, other little enzymes will come along, scoop up the remains of the virus's genetic code, cut it up into little bits, and then store it in those CRISPR spaces.

Now comes the clever part: The bacteria uses the genetic information stored in these CRISPR spaces to fend off *future* attacks. When a new infection occurs, the bacteria produces special attack enzymes — known as Cas9 — that carry around those stored bits of viral genetic code like a mugshot. When these Cas9 enzymes come across a virus, they see if the virus's RNA matches what's in the mugshot. If there's a match, the Cas9 enzyme starts chopping the virus's DNA up and neutralizing the threat. It looks a little like this:



CRISPR/Cas9 gene editing complex from Streptococcus pyogenes. The Cas9 nuclease protein uses a guide RNA sequence to cut DNA at a complementary site. Cas9 protein: red. DNA yellow, RNA blue. | (Shutterstock)

So that's what CRISPR/Cas9 does. But for a while, this discovery wasn't of much interest to anyone except microbiologists — until a series of further breakthroughs occurred.

How did CRISPR revolutionize gene editing?

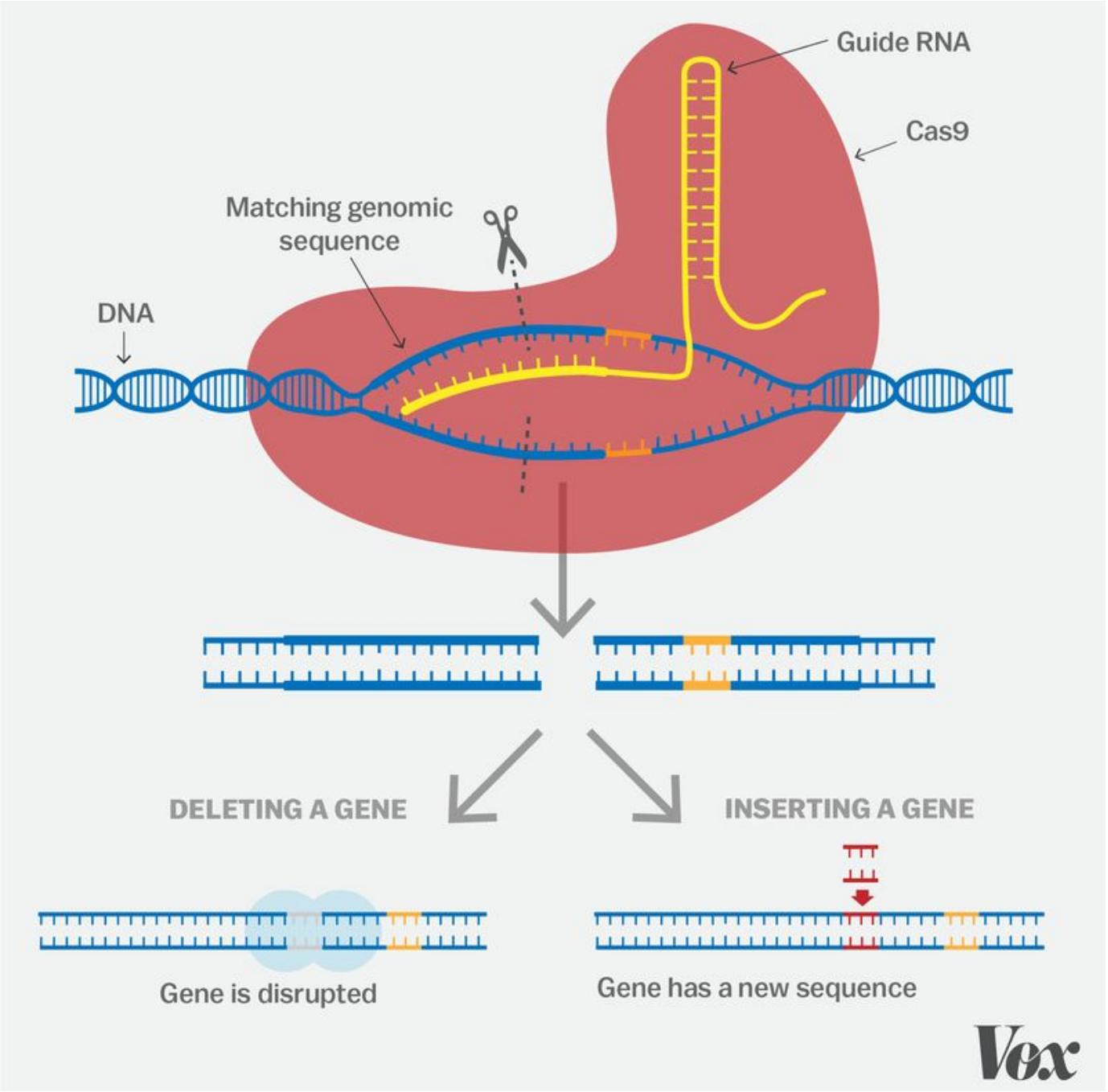
In 2011, Jennifer Doudna of the University of California Berkeley and Emmanuelle Charpentier of Umeå University in Sweden **were puzzling over** how the CRISPR/Cas9 system actually worked. How did the Cas9 enzyme match the RNA in the mugshots with that in the viruses? How did the enzymes know when to start chopping?

The scientists soon discovered they could "fool" the Cas9 protein by feeding it artificial RNA — a fake mugshot. When they did that, the enzyme would search for *anything* with that same code, not just viruses, and start chopping. In a landmark 2012 **paper**, Doudna, Charpentier and Martin Jinek showed they could use this CRISPR/Cas9 system to cut up *any* genome at any place they wanted.

While the technique had only been demonstrated on molecules in test tubes at that point, the implications were breathtaking.

Further advances followed. Feng Zhang, a scientist at the Broad Institute in Boston, **co-authored a paper** in *Science* in February 2013 showing that CRISPR/Cas9 could be used to edit the genomes of cultured mouse cells or human cells. In the same issue of *Science*, Harvard's George Church and his team **showed** how a different CRISPR technique could be used to edit human cells.

Since then, researchers have found that CRISPR/Cas9 is ridiculously versatile. Not only can scientists use CRISPR to "silence" genes by snipping them out — they can also harness repair enzymes to **substitute in desired genes** into the "hole" left by the snippers (though this latter technique is trickier to pull off). So, for instance, scientists could tell the Cas9 enzyme to go snip out a gene that causes Huntington's disease and insert a "good" gene to replace it.



(Javier Zarracina)

Gene editing itself isn't new. Various techniques to knock out genes **have been around for years**. What makes CRISPR so revolutionary is that it's incredibly precise: The Cas9 enzyme mostly goes wherever you tell it to go. And it's incredibly cheap and easy: In the past, it might have cost thousands of dollars and weeks or months of fiddling to alter a gene. Now it might cost just $75 and only take a few hours. And this technique has worked on every organism it's been tried on.

This has become one of the hottest fields around. In 2011, there were fewer than 100 published papers on CRISPR. In 2016, **there were more than 1,000 and counting**, with

new refinements to CRISPR, new techniques for manipulating genes, improvements in precision, and more. “This has become such a fast-moving field that I even have trouble keeping up now,” says Doudna. “We’re getting to the point where the efficiencies of gene editing are at levels that are clearly going to be useful therapeutically as well as a vast number of other applications.”

There’s still **an intense legal battle** over who, exactly, should get credit for this CRISPR technology — was Doudna’s 2012 paper the breakthrough, or was Zhang’s 2013 paper the key advance? The lawsuit around these patents **is currently underway**, with the fate of licensing fees worth potentially billions of dollars at stake. But the important thing is that CRISPR has arrived.

So what can we use CRISPR for?

What am I in for now. | (Shutterstock)

So many things. **Paul Knoepfler**, an associate professor at UC Davis School of Medicine, **told Vox** that CRISPR makes him feel like a "kid in a candy store."

At the most basic level, CRISPR can make it much easier for researchers to figure out what different genes in different organisms actually *do* — by, for instance, knocking out individual genes and seeing what traits are affected. This is important: While we've had a **complete "map" of the human genome** since 2003, we don't really know what function all those genes serve. CRISPR can help speed up genome screening, and genetics research **could advance massively as a result**.

But the real fun — and, potentially, the real risks — could come from editing genes of various plants and animals. A **recent paper** in *Nature Biotechnology* by Rodolphe Barrangou and Doudna listed a flurry of potential applications in the future:

1) Edit crops to be more nutritious: Crop scientists are already looking to use CRISPR to **edit the genes of various crops** to make them tastier, or more nutritious, or better survivors of heat and stress. They could potentially use CRISPR to snip out the allergens in peanuts. Korean researchers are looking to see if CRISPR could help bananas survive a deadly fungal disease. Some scientists have shown that CRISPR can **create hornless dairy cows** — a huge advance for animal welfare.

Over the past year, major companies like **Monsanto** and **Dupont** have begun licensing CRISPR technology, hoping to develop valuable new crop varieties. While this technique won't entirely replace traditional GMO techniques — which can transplant genes from one organism to another — CRISPR is a versatile new tool that can help identify genes associated with desired crop traits much more quickly. It could also allow scientists to insert desired traits into crops more precisely than traditional breeding, which is a much messier way of swapping in genes.

"With genome editing, we can absolutely do things we couldn't do before," says Pamela Ronald, a plant geneticist at University of California Davis. That said, she cautions that it's only one of many tools for crop modification out there — and the challenge of successfully breeding new varieties could still take years of testing.

It's also possible that these new tools could attract controversy. Foods that have had a few genes knocked out via CRISPR **are currently regulated more lightly** than traditional GMOs. Policymakers in Washington, DC, are currently debating whether it

might make sense to rethink regulations here. This piece for Ensia by Maywa Montenegro **delves into some of the debates** CRISPR raises in agriculture.

2) New tools to stop genetic diseases: Scientists might also use CRISPR/Cas9 to edit the human genome and knock out genetic diseases like Huntington's disease or cystic fibrosis. Scientists have even shown that CRISPR can knock HIV infections **out of T cells**.

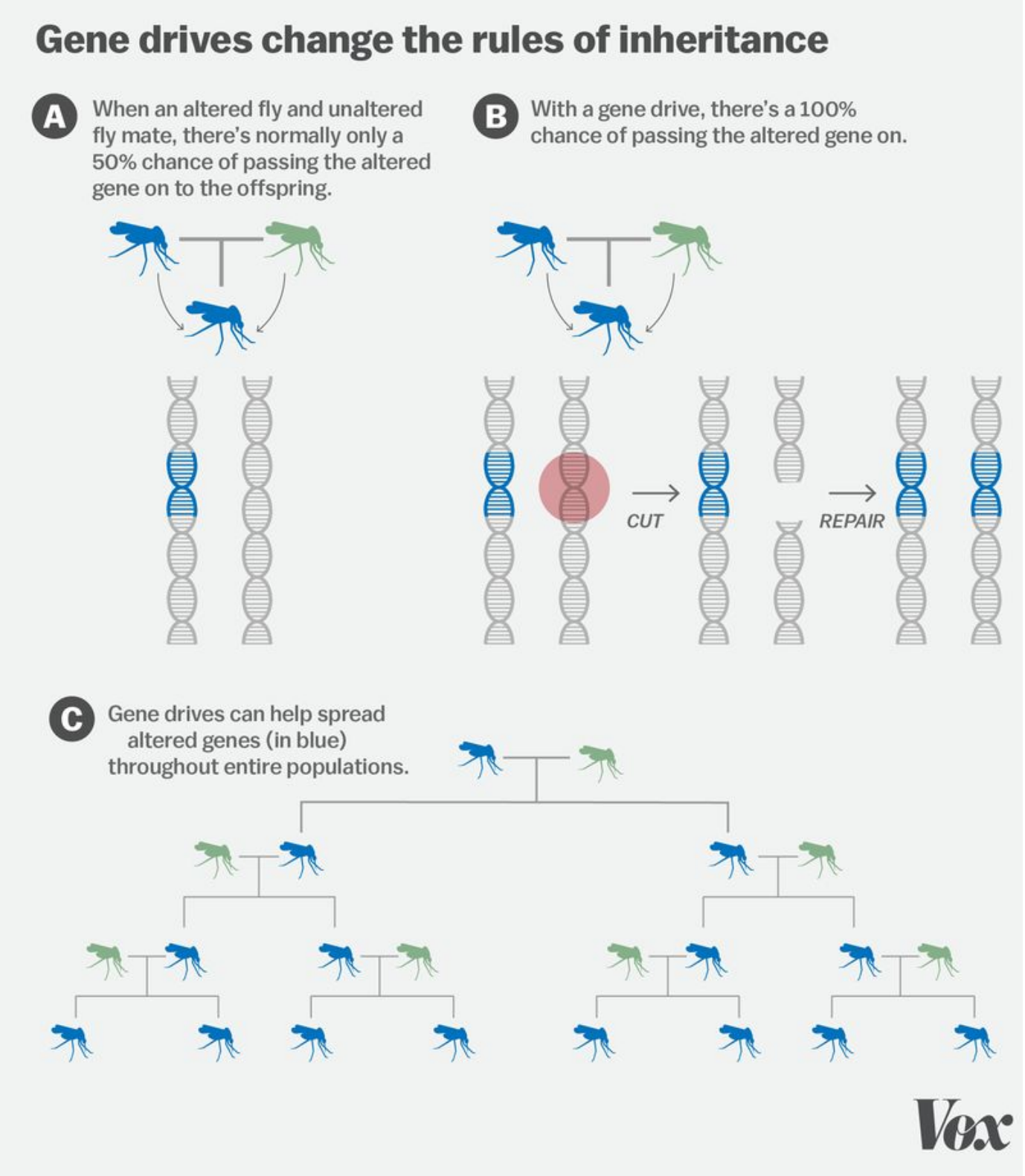
So far, however, scientists have only tested this on cells in the lab. There are still **a few hurdles to overcome** before anyone starts clinical trials on actual humans. For example: The Cas9 enzymes **can occasionally "misfire"** and edit DNA in unexpected places, which, in human cells, might lead to cancer or even create new diseases. Over the past year, **there have been major advances** in improving CRISPR precision and reducing these off-target effects, but scientists are urging caution on human testing until standards can be developed here. There's also plenty of work yet to be done in actually delivering the editing molecules to particular cells — a major challenge going forward.

3) Powerful new antibiotics and antivirals: One of the most frightening public health facts around is that **we are running low on effective antibiotics** as bacteria evolve resistance to them. Currently, it's difficult and costly to develop fresh antibiotics for deadly infections. But CRISPR/Cas9 systems could, in theory, be developed to eradicate certain bacteria more precisely than ever (though, again, figuring out delivery mechanisms will be a challenge). Other researchers are working on CRISPR systems that target viruses such as HIV and herpes.

4) Gene drives could alter entire species: Scientists have also demonstrated that CRISPR could be used, in theory, to modify not just a single organism but to modify an *entire species*. It's an unnerving concept called **"gene drive."**

It works like this: Normally, whenever an organism like a fruit fly mates, there's a 50-50 chance that it will pass on any given gene to its offspring. But using CRISPR, scientists can alter these odds so that there's a nearly 100 percent chance that a particular gene

gets passed on. Using this gene drive, scientists could ensure that an altered gene soon propagates throughout an entire population in short order:



(Javier Zarracina / Source: Oye et al 2014)

By harnessing this technique, scientists could (say) genetically modify mosquitoes to only produce male offspring — and then use gene drive to push that trait through an

entire population. Over time, the population would go extinct. Or we could modify ticks so that they don't spread Lyme, or eliminate weeds. You name it.

Suffice to say, there are lots of concerns about unintended side effects here, and the National Academy of Sciences **has recommended a moratorium** on deploying this technology until we better understand its impacts.

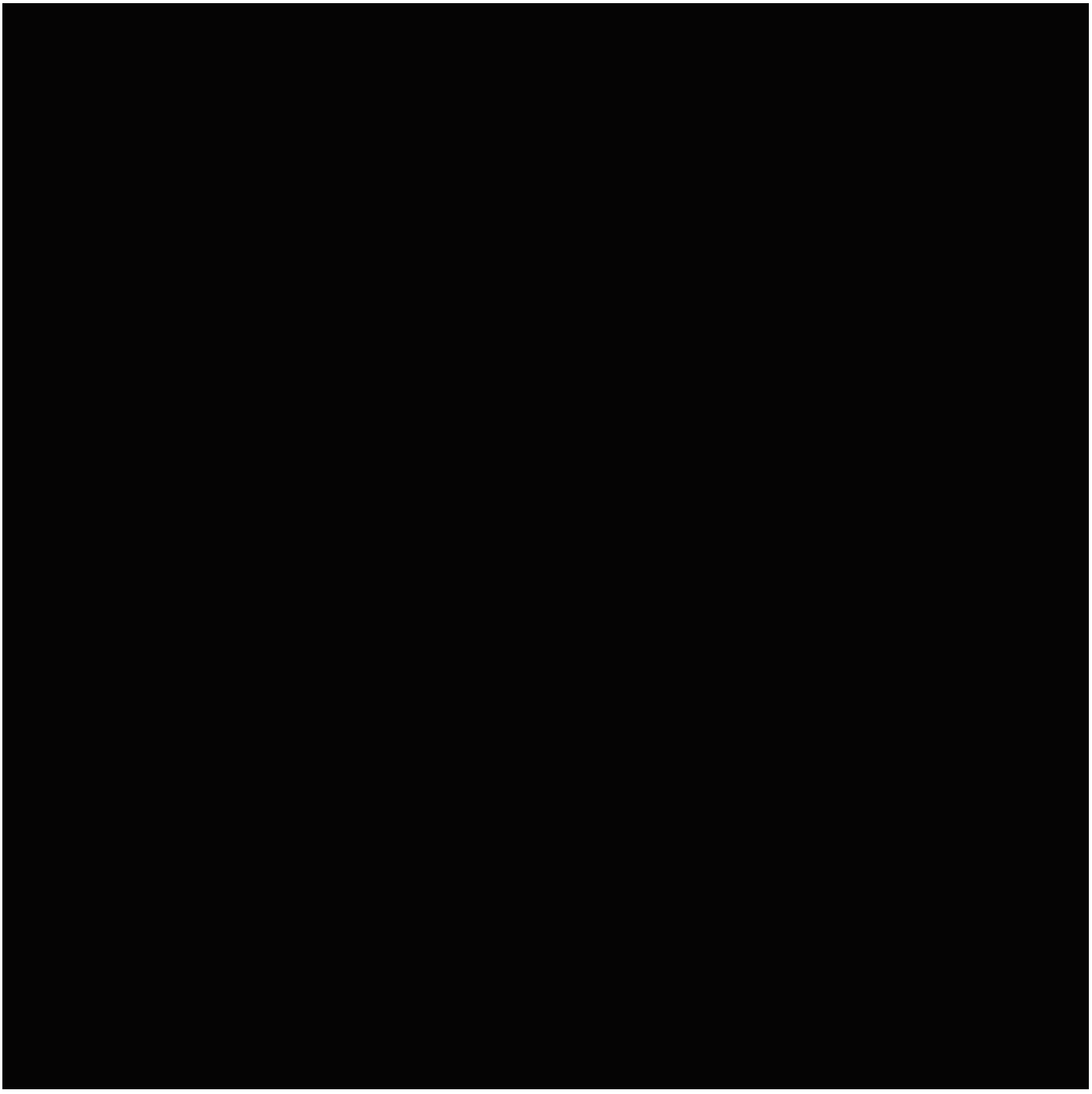
5) Creating "designer babies." This is the one that gets all the attention. It's not entirely far-fetched to think we might one day use CRISPR to edit the human genome — to eliminate disease, or select for athleticism, or for superior intelligence.

That said, scientists aren't even close to being able to do this. In April 2015, for the first time ever, Chinese researchers **attempted to edit** 86 nonviable embryos in order to remove a simple gene associated with a blood disorder called beta thalassaemia. It was a mess. Only 71 survived and only a fraction had been successfully modified. In many, CRISPR misfired or left an unwieldy mix of edited and non-edited cells. (The embryos were at no risk of becoming children, and were destroyed after the experiment.)

And that's for something as "simple" as trying to knock out a blood disorder. We're not even close to the point where scientists could safely make the complex changes needed to, say, improve intelligence. So don't go dreaming of **Gattaca** just yet.

"I think the reality is we don't understand enough yet about the human genome, how genes interact, which genes give rise to certain traits, in most cases, to enable editing for enhancement today," Doudna **told my colleague** Julia Belluz. Still, she added: "That'll change over time."

Wait, should we really create designer babies?



Can't wait to have a superhuman sister. | (Shutterstock)

Given all the fraught issues associated with editing the human genome, many scientists are advocating a go-slow approach here.

In December 2015, the Organizing Committee for the International Summit on Human Gene Editing **warned** that researchers should probably stay away from using CRISPR in clinical research to edit the human "germline" — i.e., sperm, eggs, and embryos — for now. The science is just too new. And we don't fully understand all the side effects.

What's more, the committee said, society still needs to grapple with all the ethical considerations. For example, if we edited a germline, future generations wouldn't be able to opt out. Genetic changes might be difficult to undo. There's also "the possibility that permanent genetic 'enhancements' to subsets of the population could exacerbate social inequities or be used coercively."

At the same time, the committee didn't completely rule out germline editing down the road. It also said that researchers could experiment with embryos and conduct other research around human cells, as long as they didn't "establish a pregnancy." Even this stance has worried some researchers, like **Francis Collins** of the National Institute of Health, who has said the US government will not fund any genomic editing of human embryos. In the meantime, researchers in the UK, Sweden, and China **are moving forward** with their own experiments editing nonviable human embryos.

Further reading

- Over at Stat, Sharon Begley **has been doing terrific reporting** on the legal wrangling over who should get credit for CRISPR. Her coverage is very much worth following.
- The same goes for Carl Zimmer, who has been on the CRISPR beat for a long time. His 2015 piece in Quanta is **well worth reading**.
- *Nature* **recently explored** some of the subtle limitations of CRISPR — and the search for additional gene-editing tools. And **this earlier *Nature* piece** by Heidi Ledford is a delightfully wonky dive into the ways researchers could use CRISPR to explore the genome. It's also worth **checking out this paper** listing all the different future applications of CRISPR.

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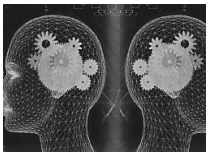

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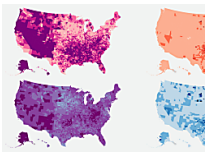

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