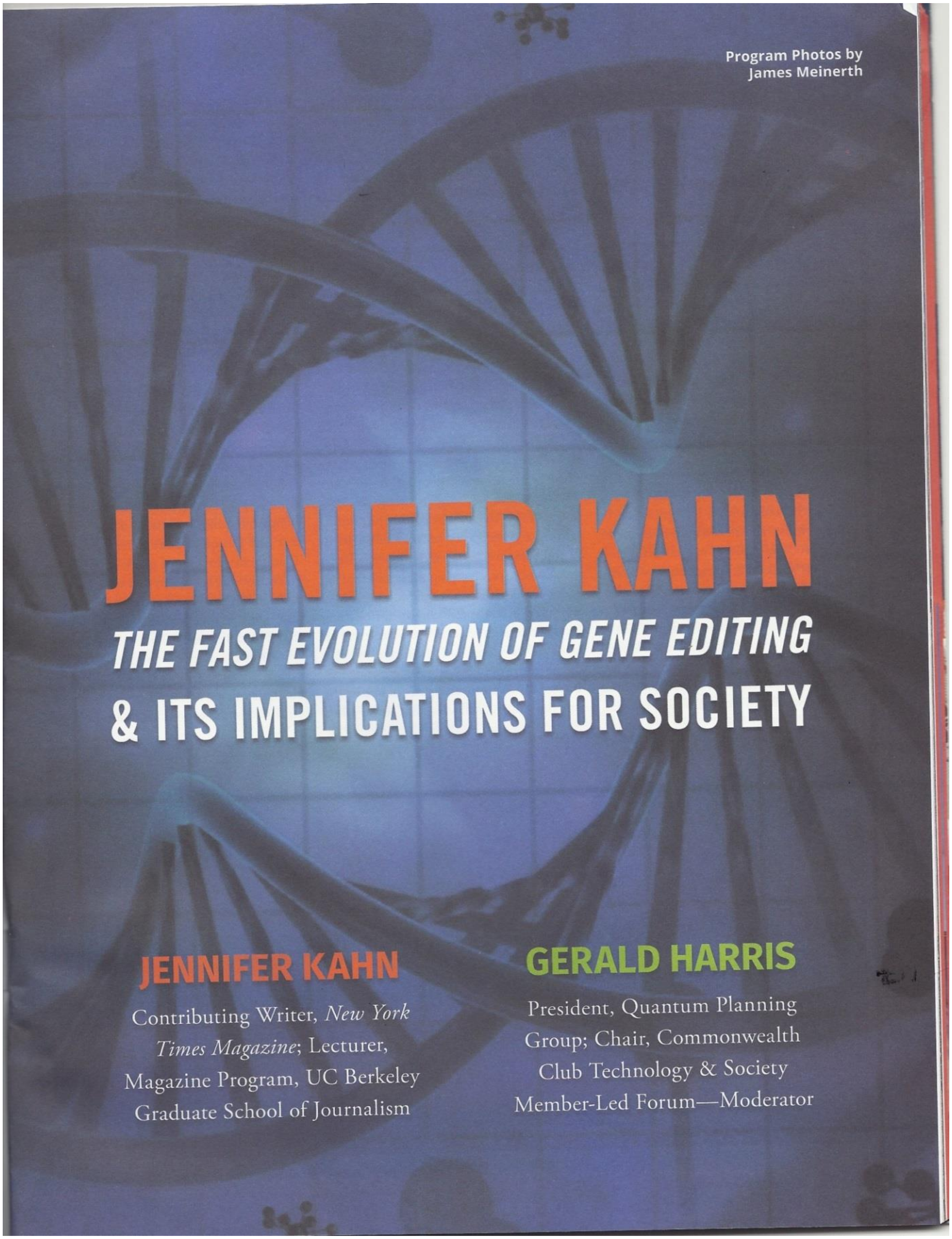

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THE FAST EVOLUTION OF GENE EDITING & ITS IMPLICATIONS FOR SOCIETY

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GERALD HARRIS: In light of the mission of the Technology & Society Forum, I can think of only a few other areas of emerging technology, perhaps AI [artificial intelligence], that is more important to inform the public about so that an informed democratic process for its use can be created and maintained. The potential uses of this technology cross many areas of our lives, and its potential to change our everyday lives is vast.

Jennifer, define the terms for us so that we can all get on the same page.

JENNIFER KAHN: First—most basic thing—the technology I'm going to be talking most about tonight is this one you've probably heard of called CRISPR. It stands for something complicated, which is Clustered Regularly Interspaced Short Palindromic Repeats. Please forget that I even said that, because it doesn't matter. But it just describes what the original gene looked like when they found it in bacteria. But since then it's actually come to mean something different, which is a tool that was developed. People found this sort of thing in bacteria, and then they were able to turn it into a tool that could edit genes.

We've been editing stuff in mice and everything for a while. But the thing I certainly didn't realize when I started writing about this was that it was incredibly hard to do this. It would be a student's Ph.D. thesis to do a single edit of one gene in a mouse and see what that did.

The thing about CRISPR is that it made it so much faster, so much easier, so much cheaper. Almost anybody could do it. One of the really powerful things it did was make it possible to just edit genes, see what they did. You could do it in a couple days instead of a couple years. That was the big difference.

HARRIS: I know there's gene editing, gene drive—so can you break those down for us?

KAHN: Actually, one thing I should make clear is an interesting thing about gene editing versus, say, GMOs, when you hear about GMO food. Gene editing just means editing a gene. Every cell has DNA in it. If you want to change those letters—like a word processor, changing the letters that are in the DNA—that's just gene editing. GMO nowadays refers specifically to introducing kind of a foreign gene. If you want to have a tomato that is resistant to frost, and you take a gene from a flounder, which has a thing that is resistant to frost, and you stick it in the tomato—they actually did this. It was called a fish tomato. Didn't really work very well. Nobody bought it. But they tried it. This was back in the '90s. So that's GMOs.

We still do some of that. It's still possible. But I think the conversation has really moved just to this gene editing, because with CRISPR there's often not as much of a need to introduce things from [other organisms]—it's called *transgenic*.

You can just edit the genes themselves.

HARRIS: As I understand gene drive, that's a little bit more complicated.

KAHN: I'm trying to take this step by step, because it is complicated, and they all use the word *gene* for some reason.

So a gene drive is different still. So a gene drive is basically just something that helps spread a trait all the way through a population. So if you have a bunch of mosquitoes, millions of mosquitoes, and say you want none of them to be able to transmit malaria, right? So gene editing just means you can take a single mosquito, you change it up, and look, that one mosquito can't transmit malaria. That doesn't do a lot of good, because now you've got one mosquito that can't transmit malaria, but you've still got 10 bazillion that can, right? So then how do you get them all to not transmit malaria?

It turns out there's a thing called a gene drive that just basically ensures that a particular trait will get inherited. So if you release, say, 1,000 of these modified mosquitoes that

Moderator Gerald Harris and Jennifer Kahn can't get malaria, and if they successfully manage to breed with all the other mosquitoes out there, it basically means that all the offspring will not be able to pass on malaria. So eventually that will actually spread throughout the entire population.

HARRIS: If I understand you correctly, if someone used gene drive on a human being, then the same thing would happen to their posterity. Is that not [what we're talking about here]?

KAHN: That's a great question. So the thing about gene drives is that in practice they only work in things that reproduce really quickly—like mice and insects. In theory, we could put a gene drive in a person, but we're people with agency, so people wait—you wait 20 years, then they have to marry someone else. I mean, it would just take forever. It takes so long, by that point, if you saw it happening, you could stop it. You could undo it, probably. So we probably don't need to worry about it happening in us, in elephants, in other stuff. But definitely stuff that reproduces kind of quickly works.

HARRIS: How much do we know versus how much [do] we think we know? As I understand it, you can change one thing in my genetic code, and it could affect thousands of things in my life. So what gives us the confidence that we kind of know what we're doing, in light of that?

KAHN: Oh, I don't think we have that confidence at this point. That's part of why you guys have—

Should I go to the CRISPR babies at this point?

HARRIS: Please do.

KAHN: This was a big thing that made a lot of news in the past six months or so. There was a scientist named He Jiankui in China who, somewhat unilaterally—there's some debate over whether there was support from the government on this or not—basically used in vitro fertilization, but within that edited a single gene in these twin girls who ended up being born.

Researchers had been doing that in embryos in the past, but certainly not taking them to term. They were just doing it to sort of see if it could be done. He was the first one who actually created children that went out in the world. The particular gene he modified was called CCR5, and he modified it because there's people out there with a natural mutation in that gene, and they're resistant to HIV. They just don't get the virus at all.

That would seem like a good thing. Why not do it?

There's a couple problems with it. Well, there's several problems, but in his case, one practical problem is it's not clear that his experiment really worked. At least one of the twins has something they called mosaicism, where the altered gene ended up in some of the cells but not [all] of the cells. That's not automatically terrible. A lot of us have some sort of mosaicism. But it means we don't even know—is that kid going to be protected? What's going to happen from that? No idea.

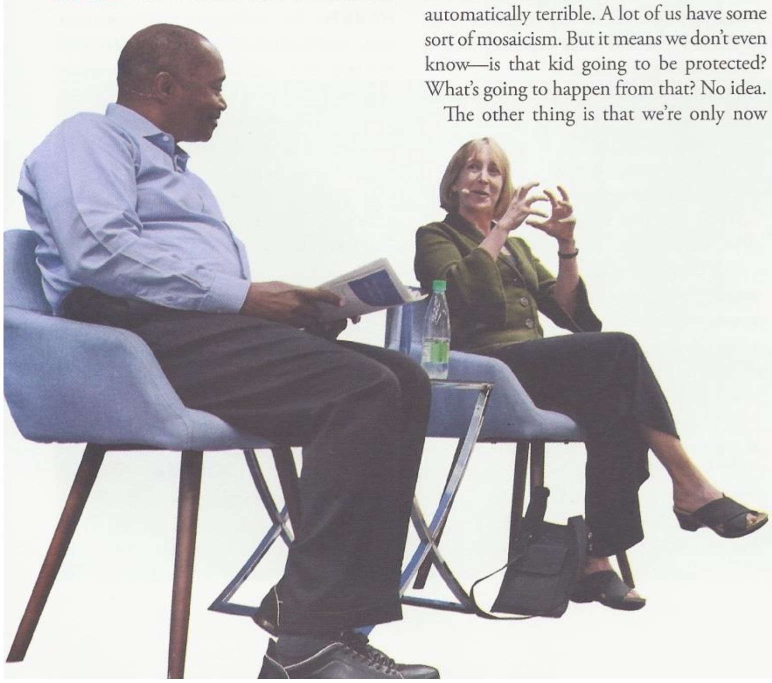
The other thing is that we're only now beginning to understand all the things that a mutation in CCR5 might affect. It might really just confer this wonderful immunity to HIV. But a recent thing they found was that people in the world who happen to have this mutation are 20 percent more likely to die before age 76 than people who don't have it. That's not great to bestow on these kids. Also, there's some indication that they're more susceptible to influenza and West Nile. So it's going to be trade-offs that make it very tricky when you do this.

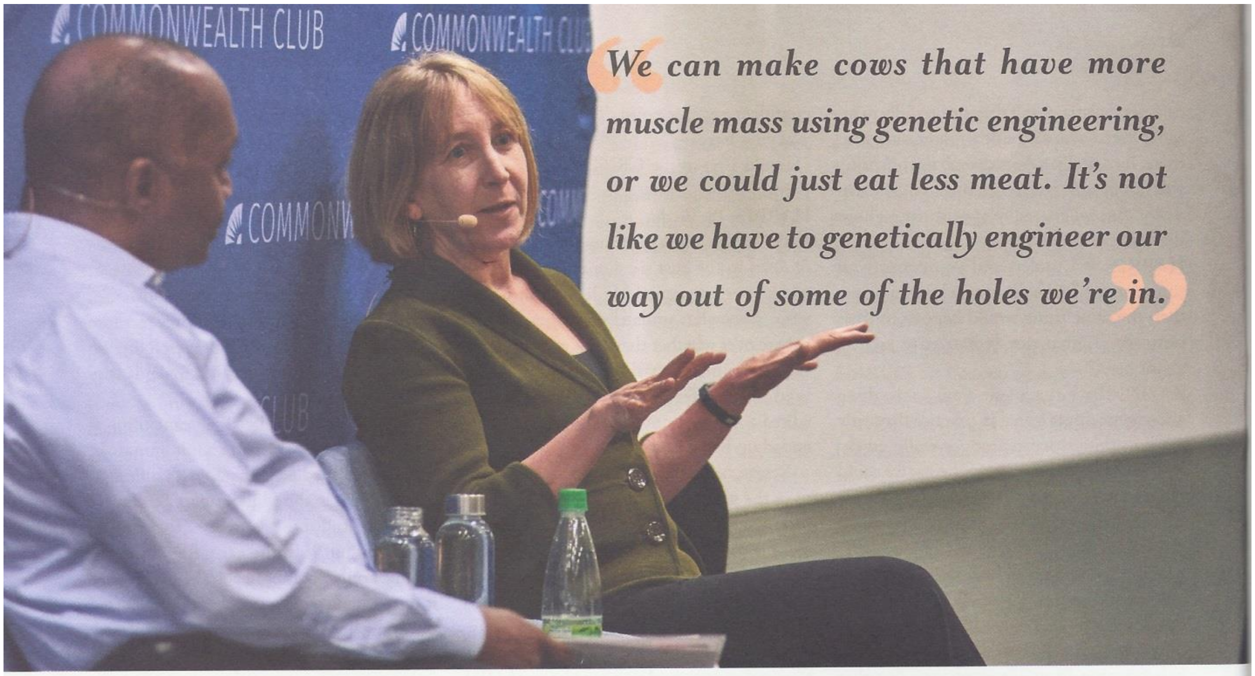
In his case, the really significant thing is that, when you do this in an adult human, in something called gene therapy, it's different. You just do it in the adult human. But he did it in what's called the germ line. They idea is, when you put it in the germ line, it means that not only are those babies going to have it, but when they have kids, it'll get passed on, and when they have kids, it'll get passed. So that's a pretty big ethical deal. You'd think we'd want to be pretty darn sure what the effect's going to be before we do it.

HARRIS: Let's dig behind that a little bit further, because there were a host of ethical [and] legal . . . I'm not even sure *how* you explain these issues. *The New York Times* did an article on this, and it exposed that certain professors from Stanford were cooperating, counseling, whatever, with this Chinese scientist, and that they had a set of rules around scientific sharing and these kinds of things that really weren't visible to the public. It wasn't clear they were being regulated; [it] wasn't clear who was enforcing it.

KAHN: The reality is that there really isn't regulation around this at this point. In 2017, the National Academies of Science, Engineering, and Medicine tried to come up with a draft thing. Like, "Oh, these are guidelines. We recommend you don't do this or that." Then, unfortunately, at the conference, He Jiankui said, "Oh no, I followed all those guidelines." So apparently these guidelines were so vague that he somehow was able to kind of think, "No, no, I'm following all the procedures correctly."

Just two days ago, there was another meeting of not just the National Academies—it's now an international consortium—and they're now trying to create a much more comprehensive and binding set of things that regulators can consult, that scientists can consult, that clinicians can consult when they're thinking about doing any of this stuff.





The problem, as I'm sure you're anticipating, is who's going to enforce this. This is a global thing. I'll say gene drive is actually kind of hard to do, but editing an embryo? It's really not that hard. It's not that hard. It's hard sometimes to have them be edited and be viable to survive, but really, this is not hard.

Something that happened after He Jiankui did his experiment. He somehow disappeared, but then a ton of clinics were writing him emails saying, "Boy, congratulations. This sounds great. When can we get access to this?" So this is from the UAE, the Middle East. People all over are looking into this. If this international consortium comes up with these guidelines, how are they going to police it? What's to stop anybody from just doing it? If you're getting national funding, maybe you can't do it. But if you're a private clinic?

HARRIS: So we don't know how we would enforce the rules even if we had them.

KAHN: Yeah. I mean, we're trying to set out good rules, and hopefully people will mostly follow them. But I feel like, at this point, it's probably something that's coming.

The one thing I will say is that, something just to bear in mind—you think about doing this, [and] the reality is it takes a long time for people to grow up. If we're talking about doing this in humans, how do we know if it's been a success or what the possible side effects are? Normally before we do these experiments we do a million experiments in mice. We might even do them in primates. And we do a lot of observation to see [what happens] in individual cells. Then, when we're pretty sure that it's safe, that's when we might try it in a person. It's never going to be 100 percent certain, but that's when you try it.

But if you just start this experiment now, we literally just have to wait until these twins grow up, and then, well, what happens? Are they going to end up dying before 76? It's actually going to take a very long time to get feedback if the way we're experimenting is experimenting on humans.

HARRIS: There are people who are convinced that the next revolution in agriculture that's going to feed the 9 to 10 billion people on the planet cannot happen without [genetic engineering in agriculture].

KAHN: The first thing I'll say is, there's plenty of things we can do that don't involve genetic engineering or gene editing. Like, for instance, we can make cows that have more muscle mass using genetic engineering, or we could just eat less meat. So it's not like we have to genetically engineer our way out of some of the holes we're in.

But that said, we are facing climate change, and that's going to affect us in the U.S. probably a bit. Probably what we'll experience is higher food prices. But globally, it can be a real disaster. You can have starvation; starvation can lead to riots; you can end up with vast climate refugees fleeing the starvation. So that can be extraordinarily destabilizing. And so if you think about it, you're going to end up having to, if you're kind of temperamentally inclined to not like the idea of mucking around with gene editing crops, you're going to have to weigh that against some of the other risks we might be facing if we *don't*—if you sort of really have an ideological objection to creating maybe a wheat that uses less water, or something like that.

HARRIS: The first agricultural revolution came with chemicals in terms of pesticides and fertilizers, and we now have all manner of side effects and externalities based on that. In California, we have all kinds of issues with the water table in terms of phosphate in the water. So can you imagine that we may have some externalities if this was widely applied in agriculture?

KAHN: Actually, there's two interesting points here: One is that we have a real habit as human beings to think about the externalities, to worry about what's going to happen, with new things, the next technology. We think, "Oh, I don't know if I should trust this." But then, as you're saying, there's all this devastation that's happened because of the overuse of pesticides. But that's the devil we know, so we tend to kind of think, "Oh, well, pesticides, we don't love them, but that's okay. But the idea of like this mucking around with genes? I don't know. I don't like that."

That said, obviously this is stuff that you want to test first. You want to make sure, for instance, if you're doing the GMO thing where you introduce a foreign gene, a thing you would want to make sure of is, what if you introduce the peanut gene? What if that might cause an allergy, or something like that? So there's stuff you definitely want to be mindful of that way.

I had a scientist explain this to me that when we crossbreed things, we're often trying to select for a particular gene. Like for years people have been crossbreeding their tomato plants to get tomatoes that are a little bigger, a little sweeter, something else, right? We just do that. What people don't realize is that when you're doing that, you may be selecting for that gene, but you're also dragging along a ton of other genes. It's very messy. It's really haphazard. The difference is, we don't see it, because we don't sequence those tomatoes. If we looked at them, we would see a ton of junk that would appall if we actually saw it in this deliberate gene editing.

What we have now is this technology that allows us to very precisely say, "Let's just change these. We know that this kind of tomato is a lot sweeter, and it has this particular series of letters. Let's just put those in." It's actually a lot more precise and a lot less messy. That's not to say there are no externalities, but it's also funny, because there's all this other stuff that somehow just because we're not aware of it doesn't bother us. *This* one, the alarming part is that we're conscious of it.

HARRIS: Let's move on to the applications of this technology for a disease an individual might have. My son carries what's called sickle cell trait, which he got from me. I got it from my father's side of the family. If he marries someone else who has the sickle cell trait, they have, I think, a 50 percent chance of creating a child that has sickle cell anemia. But recently, it seems like a young lady was treated for this and was cured. So can you talk about individual treatment and what seems to be going on here?

KAHN: Yeah, this is a really great hope. Sickle cell is a monogenic disease, which means that it's caused by a single mutation in a single gene. Imagine all the letters in your DNA, and there's one letter that somebody got wrong, and that's it. So it's a tiny thing yet immensely powerful, and the disease is awful. It's very painful. You get strokes. You die early. It's just an awful thing to inherit. And it tends to be more common in people of African descent. So far very little can be done beyond bone marrow transplants.

My understanding of this woman who was just treated: They took out the bone marrow from her, and then they took those cells, and they edited them. They edit that one letter, so now it's the right letter. That's literally all they have to do. Then they put her bone marrow back in. The bone marrow is what creates the blood cells. So instead of creating the broken sickle-shaped blood cells, it now will just create normal blood cells. So it's an extraordinary thing if it works, yeah.

HARRIS: As I understand it, there are companies in LA who are advertising that they can give your baby blonde hair.

KAHN: Oh God. Are there? I will confess, I hadn't heard about that. But I will say that one thing that actually is possible is, we've been doing IVF to select for things, so presumably you could. If they think they really have a strong genetic correlation with a particular trait—height or blonde hair, whatever it is—that's all they have to do, because they already do that. They do preimplantation diagnosis for in vitro fertilization. So it's not that hard to look at the embryo and sort of see what it's got, chuck out the ones you don't want, keep the ones you do.

Most traits aren't that simple. They might be able to select for blonde hair, but I don't think they're going to be able to select for intelligence or wit. I mean, there's many things that they're not going to be able to just sort of . . . they can't sort of promise you this stuff. Even height is actually pretty complicated.

And again, they're not. Probably, my guess—I can't imagine that they're doing any kind of editing on these things. They're just probably looking at what the sequences are and picking the one that has the blonde hair. But the problem is, because they're doing that, they're not looking at the billion other genes. So who knows if that one with the blonde hair is going to end up better, or who knows what the rest of the genes are going on in that one? So I don't know.

HARRIS: Well, you know, we Americans will pay for a lot of things. CW