* A front page with the title of the portfolio, first name/surname, teacher’s name, class name and academic year



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**CRISPR enters its first human trials**

The gene-editing technology will target cancer, blood disorders and blindness

Tina Hesman Saey

Sep 16, 2019 — 6:45 am EST

The answer to some genetic diseases may be a powerful “molecular scissors.” Known as CRISPR/Cas9, it has healed genetic diseases in some animals. Soon, doctors may learn how well it works in people. The first human studies to test its promise are just getting underway.

CRISPR/Cas9 cuts through DNA. But it doesn’t randomly chop. This gene editor comes in two parts. The CRISPR part is a short piece of genetic material called a guide RNA. Like seeing-eye dogs, these guides lead Cas9, an enzyme, to where it needs to go. Scientists can use CRISPR/Cas9 to intentionally break some genes or repair others.

In the first group of human trials, scientists are using the technique to fight cancer and blood disorders. Other researchers are set to study how CRISPR/Cas9 works inside the human body. In one upcoming trial, people with an inherited blindness will have the molecular scissors injected into their eyes.

If successful, such tests could lead to CRISPR trials for diseases affecting millions of people.

**Out of body experience**

In one pioneering trial, researchers at the University of Pennsylvania in Philadelphia are treating two people with recurring cancers. One has multiple myeloma (a disease that starts in the blood’s plasma cells). The other has a sarcoma. Both patients received a type of immune cell that had been programmed with CRISPR to go after cancer cells. (Similar trials are under way in China.)

Another trial is under way for two blood disorders: sickle-cell disease and beta-thalassemia (Bay-tuh Thah-lah-SEE-mee-uh). Both result from defects in the gene for hemoglobin. That’s the oxygen-carrying protein in red blood cells.

People who inherit a sickle-cell mutation or a beta-thalassemia mutation normally get these diseases, says David Altshuler. He’s the chief scientist at Vertex Pharmaceuticals. It’s a drug company based in Boston, Mass., and London, England. Changing a different gene may help people avoid these disorders.

In the womb, one form of hemoglobin helps fetuses grab extra oxygen from their mother’s blood. The body normally stops making this hemoglobin right after birth. But in some people, a harmless gene variant causes fetal hemoglobin to be produced throughout their lives.

People who have mutations that cause beta-thalassemia or sickle cell disease didn’t get either disorder if they also had the lifelong fetal-hemoglobin gene.

Vertex and CRISPR Therapeutics, a company in Cambridge, Mass., are now testing whether CRISPR/Cas9 can engineer changes in the body to mimic the change that keeps fetal hemoglobin turned on for life.

Both the cancer and blood-disorder trials take cells from people’s blood. DNA in those cells is edited with CRISPR/Cas9 in lab dishes. Scientists can test the cells to make sure the DNA has been edited properly. In the case of the blood disorders, CRISPR/Cas9 cuts a piece of DNA that usually helps turn off fetal hemoglobin after birth. Now the fetal-hemoglobin gene can turn on again. Doctors then return these edited cells into the sick people.

One person was given this treatment for beta-thalassemia in February. One got the treatment for sickle-cell disease in July.

**Inside job**

Other scientists are trying something much harder: editing DNA in cells that are still inside the body. Researchers will test this in people with an inherited type of blindness.

Some people have a mutant form of the gene known as *CEP290*. It causes rod cells in the eye’s retina to die, leading to blindness. In July, two companies started recruiting patients for a *clinical trial* of the gene editor.

One company is Editas Medicine of Cambridge, Mass. Editas is working with the drug maker Allergan. In their trial, CRISPR/Cas9 will make two cuts in the defective gene. This should snip out the troublesome piece of DNA.

The first people to get the test therapy will be adults who are nearly blind, says Charles Albright. He’s the chief scientist at Editas. “We’re going into arguably the most difficult patients to start with,” he says.

Small amounts of the CRISPR editor will be injected under the retina to test the treatment’s safety. Such low doses may not improve vision. But if those doses prove safe, later volunteers will get higher doses. The researchers may also test the therapy in children.

Editing as few as 10 percent of retinal cells might help restore some sight, Albright says. In animal tests, CRISPR edited up to about 60 percent of cells in mice and almost 28 percent in monkeys. The study’s authors reported their accomplishment in the February *Nature Medicine*.

Even if these first trials don’t work quite as hoped, CRISPR won’t be shelved, Albright says. “This is a technology that’s here to stay.”

“CRISPR is so intriguing,” adds Laurie Zoloth, “and so elegant.” A bioethicist, she works at the University of Chicago Divinity School in Illinois. Science, she says, just has to explore whether this new technology can live up to the hype.

**What Your DNA Can’t Tell You**

Par the-scientist.com

**Companies are selling reports about a wide range of physical, cognitive, and behavioral traits to consumers based on their genomic data, but such tests have a number of limitations.**

“Upload DNA data and know more about yourself,” promises Genomelink, anywhere from fitness-related attributes, such as longevity, pulmonary function, and job-related exhaustion, to intelligence-associated characteristics, including mathematical ability, hippocampal volume, and educational attainment. Just send over your data obtained from DNA testing companies such as 23andMe, Ancestry, or My Heritage and the California-based company will send back insight into more than 125 traits.

There are several other companies that provide consumers with reports about physical, cognitive, and behavioral traits based on their DNA data. Some, like GenePlaza, Helix, and Sequencing.com, have launched genetic app stores where users can choose from a variety of products. The cost of these tests varies significantly: The most expensive app on GenePlaza is €6 ($6.50 US), while Helix’s range from free to more than $200. For $14 a month, Genomelink sends users one new trait report per week.

Right now, [these reports are] more just for entertainment and to understand the limitations. I think the main benefit is engaging people with genetic research.

— Yaniv Erlich, DNA.Land

To generate trait reports, these companies typically compare a user’s DNA to data harnessed from published genome-wide association studies (GWAS). Want to know about your propensity for loneliness? Genomelink uses data from a 2018 *Nature Communications* study that examined this trait in more than 450,000 UK Biobank participants. Genomic researchers are constantly publishing new findings, says Tomohiro Takano, one of Genomelink’s founders. “So when we started Genomelink, we were wondering, how can we bring the positive and entertaining side of science directly to consumers?”

While direct-to-consumer (DTC) trait tests may be increasingly popular, their utility remains an open question. “There are many layers of unvalidated science,” says Catherine Bliss, a sociologist at the University of California, San Francisco. “[Consumers] get a lot less reliable information than they think they’re getting.”

**The limits of GWAS**

GWASs allow scientists to estimate the combined effects of single nucleotide polymorphisms to generate polygenic scores, which provide an estimate of how likely it is that an individual will develop a certain trait. Polygenic scores are widely used in scientific research, but they come with a number of limitations that are important to consider in the context of DTC tests.

There are two key issues when it comes to predicting traits with DNA data, according to Daniel Benjamin, a behavioral economist at the University of Southern California. One is that there is very little scientific evidence to support predictions for certain phenotypes, including many associated with fitness or parenting behaviors. On the other hand, even for traits that scientists have carefully examined in large GWASs, such as educational attainment, polygenic scores are typically only useful for predicting differences between groups. “That’s what makes them useful in research,” Benjamin explains. “But for the purpose of predicting what any particular individual’s phenotype is going to be, the predictive power is very low.”

To prevent people from misunderstanding the data from their own GWASs on cognitive and behavioral characteristics, Benjamin and his colleagues in the Social Science Genetic Association Consortium (SSGAC) set up a detailed FAQ page to accompany their papers. People often misinterpret the idea that genetic factors are associated with certain traits as meaning that they explain intrinsic biological differences in ability, Benjamin says. But genetic factors can matter for purely social and environmental reasons. For example, if scientists tried to predict educational attainment from DNA during a period when females faced greater barriers to obtaining schooling, the number of X chromosomes would likely be one of the strongest predictors of education attainment—due to circumstance, not biology.

In addition, most of the large GWASs have been conducted in individuals of European descent. For this reason, it’s not yet clear whether the results will be relevant for other populations, says Andrea Ganna, a geneticist at the Institute for Molecular Medicine Finland. On top of that, large datasets in the UK, such as the UK Biobank, have dominated these studies, Ganna adds. “So how this work translates to other populations, even within Europe, is an [open] question.”

Tests for traits like intelligence come with the added issue of potential ethical and societal implications. “There’s two schools of concerns,” says Yaniv Erlich, the co-creator of DNA.Land, a research-project-turned-independent-company that provides free trait reports to consumers. “One is that we predict intelligence so badly that the reports are useless. The other is we can predict it so well that people can start to discriminate based on these reports.” While the field is currently facing the former problem, according to Bliss, there are already people, including some scientists and educators, who see the utility in using such tests to guide children’s futures.

**Maintaining transparency, educating consumers**

Given these shortcomings, why provide such tests at all? “At this point, we are purely focusing on the user having a positive, fun experience—we are not asking users to take any action,” says Genomelink’s Takano. “My philosophy is that, the information is already available, so rather than hiding that, we want to try to educate people so that they can understand the limitation of the science.”

It’s a good thing that these companies have disclaimers, but it’s not enough.

—Daniel Benjamin, University of Southern California

Takano says that his company tries to be as transparent as possible to its consumers. Its trait reports come with “scientific reliability” ratings based on the robustness of the reference literature, as well as a description of the underlying research. Genomelink also provides a brief explanation on the FAQ page about how limitations in the science may lead to inaccurate results. (A more in-depth description is provided in an accompanying blog post.)

Other companies also provide consumers with information about their products’ limitations. Geneplaza, whose apps include reports about ancestry, intelligence, and same sex attraction, has a disclaimer on most of its apps, along with some information about the underlying science. “We try to stress the fact that this is not a disposition score, it’s not a diagnostic,” says Alain Coletta, cofounder and CEO of GenePlaza. “We hope we’re doing a good enough job but it’s not easy to do.”

Erlich notes that he and his colleagues at DNA.Land chose to primarily provide reports for physical features, such as height and eye color, so that people could easily verify whether or not the genetic predictions were correct. On the other hand, he adds, they launched their intelligence report to have the opposite effect. “We aim to show you that we cannot predict intelligence in any meaningful way,” says Erlich, who is now the chief scientific officer at MyHeritage. “Right now, [these reports are] more just for entertainment and to understand the limitations. I think the main benefit is engaging people with genetic research.”

In principle, if consumers understand the limitations of polygenic scores, finding out your genetic prediction for a given trait could be a fun activity, Benjamin says. “But my worry is that they won’t understand the information they’ve been given.” He adds that one thing that’s currently missing is research into how best to present these types of disclaimers, and how well people comprehend this information when it’s presented clearly. “It’s a good thing that these companies have disclaimers, but it’s not enough,” Benjamin tells *The Scientist.* “People have to actually understand the information.”

*Diana Kwon* *is a Berlin-based freelance journalist.*

**Gene Editing Humans: It's Not Just about Safety**

Par Mildred Z. Solomon

blogs.scientificamerican.com



Chinese scientist He Jiankui surprised the scientific community and the world when he announced in November 2018 that he had genetically modified two embryos and then allowed them to develop into babies. Not only that, he believed he had acted in accordance with guidelines offered by a 2017 report by the National Academies of Sciences, Engineering, and Medicine.

More recently Denis Rebrikov, a Russian scientist, announced his intention to edit a human embryo and implant it in a woman, allowing it to develop. These renegade scientists have prompted what STAT News called a “do-over” by the National Academy of Sciences, the National Academy of Medicine and the U.K.’s Royal Society.

Last week these organizations convened the first of a series of important meetings of their jointly sponsored International Commission on the Clinical Use of Human Germline Genome Editing. In addition, the World Health Organization has formed an Expert Advisory Committee on Developing Global Standards for Governance and Oversight of Human Genome Editing.

These groups are aiming to be much clearer this time around and to establish a governance framework so that scientists such as He and Rebrikov will understand and respect the guidelines that their peers have established: human germ-line modification is not yet safe. Because there are still many unresolved issues, including so-called off-target results, partial edits and other problems, basic bench gene-editing research can go on, so long as embryos are not allowed to develop.

Even as these bodies regroup to produce clearer guidance, however, I sense a shift in the debate. For a very long time, the scientific and bioethical consensus was that we must not do human germ-line modifications—that we should not change gametes and embryos in ways that would be permanent, affecting all future generations. In contrast, somatic modifications, which affect only the person in whom the edits are made, have been mainly uncontroversial.

But that border between germ-line and somatic genome modification is blurring; the zeitgeist feels different. There is a growing sense of inevitability that we will eventually do human germ-line modification and that our only obligation is to wait until it is safe. When that day comes, we may want to make permanent heritable changes to the human species to eradicate otherwise intractable diseases. We should, however, enter this discussion with eyes wide open, considering each application on its own merits and anticipating a wide range of issues that go well beyond safety. Many of these issues are explored in *Human Flourishing in an Age of Gene Editing,* which will be published by Oxford University Presson August 28, 2019.

Although we do not yet know the genetic predictors of many conditions, as we learn more, the temptation to use gene-editing technologies to “enhance” ourselves will be extraordinary—and particularly problematic if we gain the ability to reduce the likelihood of highly stigmatized traits, such as homosexuality, or to edit in highly desirable ones, such as tallness or athleticism. Many parents will, perhaps legitimately, assert that they are not prejudiced against homosexuality, or some other way of being, but just think that it makes life harder. So why not edit out the genes that increase the odds of it occurring? And don’t all good parents strive to give their children advantages?

Many of the choices coming our way will be ones that should rightly reside with prospective parents. But even when decisions are personal and private, they should be well informed, which is why we need far more ways to engage the public in conversations about germ-line genome editing. Vigorous community discussion of the values at stake is necessary for truly informed personal decision-making.

We need broad community conversation on issues beyond safety for another reason, too. What people choose to do on their own can change the collective, even when those changes were not intended for the population as a whole. Human germ-line genome editing is the quintessential example of a technology that will have both personal and collective impacts, affecting our shared environment.

How, for example, might the ability to select the features we want in our children affect the relationship between parents and children and the virtues we want to see in our communities? Commentators such as Michael Sandel of Harvard University have warned that control over the genomes of our children could lead to a sense of “hyperagency,” whereby we would lose the sense of children as gifts to be nurtured as they come to us and rather see them as objects we have designed. Will children who have been edited to have greater musical talent or athletic prowess feel obliged to fulfill their parents’ dreams even more than children usually do?

Moreover we could craft our progeny on the basis of popular but suspect norms such as homophobia or certain physical features. We could also inadvertently set up what some commentators have called a “genetic arms race,” in which parental attempts to give children an advantage just leave everyone competing at ever higher levels of whatever trait is being sought.

Surely such control is a long way off, but we are now charting a path toward human enhancement that might ultimately reduce variation in the species or, over a long period of time, lead to subspeciation. Indeed, transhumanists advocate exactly that result—a melding of new biological and synthetic powers that will essentially change the very nature of our species.

We need forums and strategies for discussing beyond-safety implications: books for scholars, policy makers and interested members of the public that will anticipate the wide array of social, economic and ethical implications of enhancement: educational experiences for students and their teachers; literature and films that do not sensationalize but help us consider the social and ethical complexity of our newfound powers; deliberative polling and other forms of democratic deliberation; and multiple channels of communication between experts and nonexperts.

Both the international commission and the WHO’s committee promise to review a wide range of social and ethical issues, well beyond safety. I hope they stick to that intention. Their meeting last week got off to a great start, with calls for more scientific transparency and renewed commitments to generating a global framework to establish parameters for this research.

But it will take sustained courage to address all of the implications of this technology. In a pluralistic society, it can be frightening to open the Pandora’s box of discussion about deeply held values. With so many different views that are seemingly impossible to reconcile, it will be easier to focus only on safety, which is the bare minimum that just about everyone can agree on. But we avoid the larger, harder conversation at our grandchildren’s peril.

The views expressed are those of the author(s) and are not necessarily those of Scientific American.

* A conclusion to explain what you have learned/thought while putting together the portfolio (max. 200 words)

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