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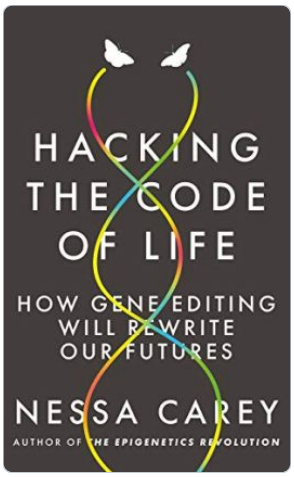

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Hacking the Code of Life

How Gene Editing Will Rewrite Our Futures

Nessa Carey • Icon Books © 2019 • 176 pages

Science / Biology / Genetics / Genetic Engineering

Take-Aways

- The latest gene-editing techniques will transform the biological sciences.
- Human beings have always practiced forms of genetic modification.
- In the 1970s, scientists began to learn how to modify genes directly.
- In the 21st century, gene editing finally became practical.
- Gene editing could revolutionize the cultivation of food crops.
- Gene editing may also alter livestock and other animals.
- Eventually, scientists may apply gene-editing technology to humans.
- Researchers will need to verify that the technology is safe.
- Society should debate the ethics of gene editing now.
- Gene editing is likely to be commercially important.

Recommendation

The breakthrough in gene editing known as CRISPR may offer cures for genetic disease, new treatments for cancer, and healthy new food crops that are resistant to pests and droughts. This raises fears of a new eugenics or an ecosystem catastrophe. British biologist Nessa Carey provides a concise guide for laypeople to the history and mechanics of gene editing and outlines its promise in agriculture and medicine. Her basic approach makes for a quick, easily digestible introduction to this burgeoning field.

Summary

The latest gene-editing techniques will transform the biological sciences.

In 2012, scientists unveiled a new genetic-modification technique that could revolutionize science and propel major advances in medicine and agriculture.

> *"We are entering the era of gene editing, and the game of biology is about to change. Forever."*

With this new technology, scientists can modify the genome of organisms with unprecedented precision. Compared with previous techniques, the new gene-editing technology is fast, cheap and easy to use.

Human beings have always practiced forms of genetic modification.

Long before people knew what genes were, they crossbred plants and animals to increase their desirable traits.

> *"It's remarkable to consider that almost all human activity – glorious or disastrous and everything in between – has been built because we have learned how to hack the genetic material of other organisms."*

In the 19th century, Gregor Mendel undertook the first systematic efforts to understand the mechanisms that underlay breeding. Mendel performed extensive experiments in crossbreeding pea plants and recorded the results. He speculated that what he termed "invisible factors" must govern how organisms passed traits to their offspring. Decades later, botanist Wilhelm Johannsen named these invisible factors "genes." Scientists didn't know what genes were made of until 1944, when Oswald Avery determined that the construction material was deoxyribose nucleic acid (DNA). In the 1950s, scientists James Watson and Francis Crick, building on data compiled by Rosalind Franklin, outlined DNA's double-helix structure.

In the 1970s, scientists began to learn how to modify genes directly.

Scientists Stanley Cohen and Herbert Boyer took genetic modification beyond the trial-and-error efforts of plant and animal breeding. They learned to remove specific genetic material from one organism and insert it into the genome of another – even from a different species – whereby the material would continue to

perform its intended function. This opened the door to using genetic engineering to treat human diseases and alter food crops.

> *"For the first time in Earth's history, one species has the capability to alter the genomes of other living organisms, including itself."*

But the process was unwieldy, expensive and time-consuming. Inserting genes exactly where a scientist wanted them to go proved challenging. In 2012, scientists announced the breakthrough that promised to make gene modification easier, cheaper and more precise.

In the 21st century, gene editing finally became practical.

The new technique, called CRISPR (clustered regularly interspaced short palindromic repeats) had its roots in the work of PhD student Francisco Mojica, who had investigated odd-looking sequences in a bacterial genome. These consisted of a 30-letter sequence that repeated itself identically a number of times. Between each repeat was another sequence, which Mojica called a "spacer." The spacers were all different, and each comprised a unique series of about 36 DNA letters. Mojica established that the spacer sequences matched sequences from various types of viruses. He determined that the bacteria were immune to infection from viruses with matching sequences.

Later work by Mojica and others showed that when a bacterium suffered a viral infection, it copied a part of the virus's genome and stored it as a spacer. If the bacterium suffered a subsequent infection by the same type of virus, it would produce a duplicate of the relevant spacer, which would bind to a similar sequence in the viral genome. Once attached to the viral genome, it delivers a protein that destroys the viral DNA.

The labs of Jennifer Doudna and Emmanuelle Charpentier devised an elegant technique for co-opting this process to target a region of DNA precisely. A scientist can replace the bacterial spacer with a sequence of his or her choosing and use this to target an exact region of DNA. Once the sequence reaches the specified region, it uses the bacterial protein like molecular scissors to snip apart the DNA double helix. The cell moves to repair the DNA, usually by quickly and somewhat sloppily fusing the two ends back together. When this is all done, the gene usually loses functionality. Turning off a gene this way is useful for studying what specific genes do and may be useful clinically to shut down a patient's dangerous mutated genes.

Subsequent refinement improved the precision of gene editing to the degree that scientists can change one letter among the billions in the human genetic code. Scientists can modify the amount of proteins or other molecules that a gene expresses.

Gene editing could revolutionize the cultivation of food crops.

Global agriculture faces the challenge of producing enough crops to feed the burgeoning global population without wreaking environmental havoc. The biggest conundrum is how to do so in the face of the developed countries' worst dietary habits: overconsumption – that is, a reliance on meat and a culture of wastefulness. Perhaps gene editing can boost crop yields and enhance the nutritional value of food crops.

> *"Once you have gene-edited plant cells successfully, it can often be fairly straightforward to propagate lots of identical plants."*

Gene editing with plants has found success in several areas:

- **Reducing waste** – Grocery stores routinely toss out or reject foods that fail to meet standards of appearance. Gene editing may be able to enhance the appearance of fruits and vegetables without undermining taste or some other quality, which can always happen with traditional breeding methods.
- **Removing potential harmful food constituents** – Some food elements are unhealthy for people with certain conditions. For instance, people with celiac disease are unable to tolerate certain gluten proteins in wheat. A research group in Spain has edited wheat genes so the plants stop producing the specific types of gluten proteins that trigger a celiac response.
- **Reducing costs** – The flavors of some recipes can require expensive ingredients. Gene editing may be able to produce cheaper substitutes. Researchers at the University of California, Berkeley, applied this approach to brewing beer. Conventionally, beers derive their taste from costly hops, but researchers genetically modified brewers' yeast to deliver the same flavor.
- **Boosting yields** – Rice can grow in the midst of adverse conditions, a quality derived from past crossbreeding, but this reduces yields. With gene-editing techniques, scientists created hardy rice while increasing yields up to 31%.
- **Adapting to deteriorating environmental conditions** – Other crops must contend with farmland that is becoming increasingly arid and saline. Scientists are using gene editing to modify crops so they thrive in these conditions.

These new crops may never make it to market. The regulatory and consumer backlash against previous genetically modified (GM) foods offers little reason for optimism. At present, regulators take inconsistent approaches. The US Department of Agriculture has ruled that it won't regulate gene editing of crops if the editing produced a modification that does or could occur in nature. UK officials made gene-edited foods subject to the same strict rules that the government had placed on GM foods.

Gene editing may also alter livestock and other animals.

Gene editing could create disease-resistant animals or animals that produce more meat. The regulatory situation regarding meat from gene-edited animals remains murky, but it appears unlikely that these products will come to market any time soon.

> *"With the advent of gene editing, we can use animals in more sophisticated ways than ever before to create therapeutic drugs for human conditions."*

Gene editing may play an important role in the use of animals in medical treatments. Scientists could modify animals for use in producing a class of drugs called "biologicals." Pharmaceutical companies can't synthesize these drugs; they must cultivate them in living cells. Scientists might use gene editing to modify animals such as pigs so their organs are safe for transplanting into human beings.

Eventually, scientists may apply gene-editing technology to humans.

Scientists have been able to edit human cells but only cells already removed from the body. Now they must learn whether they can use editing technology inside living people. The first targets for this research are likely to be genetic blood disorders, such as sickle cell disease, a painful genetic condition in which the red blood cells become distorted. One way to treat this would be to remove stem cells from a patient's bone marrow and edit the cells' DNA. Scientists expect that after they reinsert altered cells into the marrow, the cells will produce healthy versions of red blood cells for years.

Other promising areas for human gene editing are the so-called privileged sites of the body that don't require donor matching – for example, the cornea. One obstacle in editing human DNA is delivering the gene-editing "reagents" into the body. They may stimulate the immune system, which regards them as foreign invaders to eliminate. But privileged sites, such as the eyes, are separate from the immune system and should make an excellent location for editing. This approach may be able to repair certain types of blindness.

> *"In theory, it should be possible to use this technology to stabilize and even reverse various forms of blindness."*

Gene editing may have a substantial impact on the treatment of cancer. In one technique, scientists can edit cancer patients' immune cells to boost their cancer-fighting power. One trial of this approach focused on children with cancer who were unresponsive to conventional treatment. After the genetic modification, 27 of 30 of the patients became cancer-free.

Researchers will need to verify that the technology is safe.

Some researchers worry that even a successful edit could cause collateral harm. Recently, researchers focused on issues surrounding a protein called p53. This protein's job is to induce cells to destroy themselves if they incur damage that could lead to cancer. Problems arise when the cell interprets gene editing's cutting of DNA as damage. The cell's efforts to limit the damage could include activating p53. This raises concern that scientists would enjoy the most success editing cells with a weak p53 response. As a result, they may be increasing the number of cells that are more likely to become cancerous.

Another area of potential risk involves the problem of unintended consequences. One editing technique can initiate what's termed a "gene drive" – a genetic change that will spread rapidly through a population. Theoretically, science could introduce a deadly mutation into mosquito genes, let the change spread through the population and thus wipe out an entire mosquito species. Eliminating these pests and the deadly diseases they carry would be a benefit. The danger is that gene drives are difficult to stop. Past incidents of human intervention in ecosystems show that the side effects such changes generate remain unpredictable.

Society should debate the ethics of gene editing now.

Scientists and larger society must grapple with the important issues that will arise from gene-editing technology. For example, consider the questions that would surround the use of gene editing to prevent inherited disorders, such as Huntington's disease or the devastating Lesch-Nyhan syndrome.

In these situations, clinicians would use in vitro fertilization and edit the DNA of the zygote to correct mutations associated with the disease. After the clinicians implanted the zygote in the mother's uterus, it would grow into a human being free of the dangerous mutation. The corrected version of the genome would then pass on to subsequent generations.

> *"It's...hoped that open discussions of the ethical and legal implications of gene editing of the human germline will increase the chances of developing frameworks that are consistent across international boundaries."*

Such interventions remain theoretical but raise ethical dilemmas. One of the most prominent is the issue of informed consent. In ethical medical practice, a clinician explains a proposed procedure to the patient, outlining its potential benefits and risks. The patient must give consent before the procedure takes place. With the proposed editing, clinicians will perform the procedure on a "bundle of cells" that can't provide consent. The results of the procedure will affect all potential subsequent generations – who have no say in the matter.

Gene editing is likely to be commercially important.

Investors have plowed around $1 billion into the main companies that specialize in gene editing: Caribou Biosciences, CRISPR Therapeutics and Editas Medicine.

> *"One of the reasons why the new gene-editing technologies are having such an impact in basic science is because they can be applied to just about any species really easily and cheaply."*

How this will all play out depends on the patent battle among the institutions that employ the three scientists who pioneered the field: Jennifer Doudna at the University of California, Berkeley; Emmanuelle Charpentier at the University of Vienna; and Feng Zhang of the Broad Institute in Cambridge, Massachusetts. Whoever ends up owning these patents could earn billions of dollars in royalties.

Caribou Biosciences is privately held, but Editas Medicine has a stock valuation of $1.2 billion and CRISPR Therapeutics enjoys a valuation of $2.6 billion.

About the Author

British biologist **Nessa Carey**, PhD, is a visiting professor at Imperial College, London, specializing in molecular biology and biotechnology. Her other books include *The Epigenetics Revolution* and *Junk DNA: A Journey Through the Dark Matter of the Genome*.