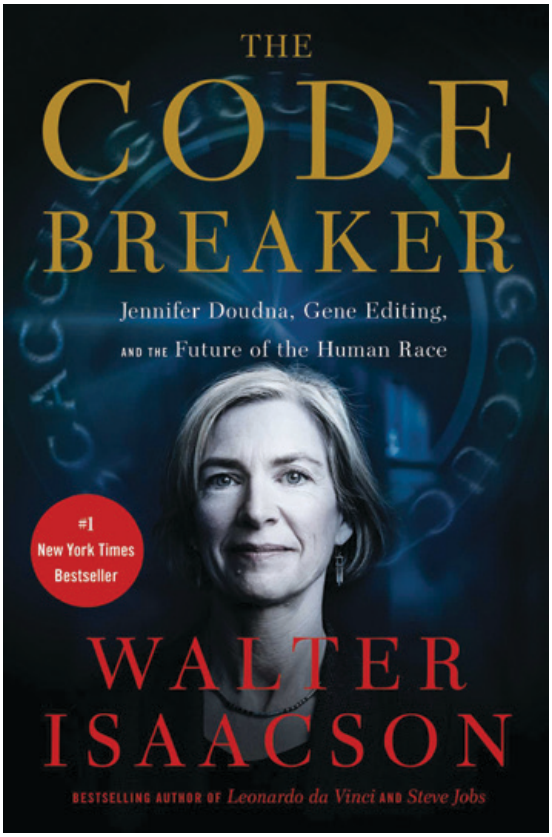
# We Haven't Really Cracked the Code of Life

JAG BHALLA

To say that scientists now understand life's "code" is a stretch. So, from the very title of Walter Isaacson's latest biography, *The Code Breaker: Jennifer Doudna, Gene Editing, and the Future of the Human Race,* he's off to a rocky start. And that isn't the only conceptual gap papered over by this beautifully built behemoth. To suggest that Doudna is a "code breaker" is to compare her to, say, the British code breakers of World War II who cracked the notorious German Enigma code. But when it comes to DNA, our code breaking isn't all it's cracked up to be: if the Allies had had the same level of expertise in actual cryptology that scientists now have with DNA, they might well have lost World War II.

*The Code Breaker* contains 481 pages of Oscar-level cinematic prose, providing a whistle-stop tour of how Jennifer Doudna, a biochemist at the University of California, Berkeley, and a large supporting cast discovered and developed the gene-editing technology known as CRISPR—an acronym for clustered regularly interspaced short palindromic repeats. These repeating DNA features were found to be part of the defense system that bacteria have evolved over their billions of years of warfare with viruses. Enzymes associated with CRISPR sequences cut up attacking viral DNA and insert a section of it into the bacteria's own genome in order to recognize it in the future. Doudna and her colleagues' innovation was to configure and use this viral "mugshot" system to target and insert specific genetic sequences, creating a flexible DNA cut-and-paste tool.




**The Code Breaker: Jennifer Doudna, Gene Editing, and the Future of the Human Race**
*by Walter Isaacson. New York, NY: Simon & Schuster, 2021, 560 pp.*

Isaacson deftly dramatizes science-in-action vignettes, with surprisingly few pages devoted to Doudna's journey from being told by a school counselor that "girls don't do science" to scientific stardom. The reader will feel like a fly on the wall at eureka moments, in lab races, dueling presentations, and patent battles. The apparently enormous market of readers who require novelistic details in their nonfiction—such as the kind of sandwich over which history-making discussions about recombinant DNA happened (pastrami)—will be thrilled.

Isaacson, the author of several bestselling books, including biographies of Steve Jobs, Leonardo da Vinci, and Albert Einstein, is the rare raconteur who can enliven complex science and the people and history involved in its making. His masterfully edited jump-cut montages of awe-stirring scenes, sneaky ego battles to steal scientific credit, and criminally gene-edited babies won't disappoint.

But the book epitomizes a kind of pop science game of telephone that isn't merely harmless fun. Isaacson's narrative falls prey to a three-step whisper-chain of information that's common in scientific storytelling. The first step is what experts say and mean given their deep background knowledge of their fields; the second is what science writers and journalists grasp and choose to highlight; and the final step is what nonexpert (and often overtrusting) readers take away. Through this process, the information that makes it into prestigious books like Isaacson's (mis)shapes the public imagination and strongly influences the thoughtscape in which policymakers and citizens operate. Although Isaacson admirably

wrestles with technical and moral complexities, I argue that his tone and balance generate a highbrow "CSI effect"—ill-founded beliefs resulting from (over)dramatic license and the elevation of entertainment above accuracy.

When Isaacson writes that scientists have cracked the "code of life" and can do "precise" gene edits, those statements are true only in a narrow sense; more broadly, they mislead. When molecular biologists use words such as "editing," "engineering," "coding," "programming," and "mapping," they generally know—or at least should know—that these are limited metaphors. In ordinary usage (i.e., outside biology), those words involve systems in which all the parts and roles are well understood. But that's not remotely the reality in the fields of genetics and molecular biology. Although it's rarely advertised, computational biologist Lior Pachter argues, "the reality is that we have no idea how the genome functions, or what the vast majority of genes or variants actually do." Isaacson does little to clarify this confusion or to counter the field's glamorous hype-fest.

Saying we're "learning the language in which God created life," to quote from President Bill Clinton at a White House event celebrating the Human Genome Project, hints at a handier analogy. This god language of the genome is written in a script that scientists can transcribe into English letters (A, C, T, and G). But researchers know what only a small fraction of the resulting words mean. Most of the approximately 20,000 entries in the human genome "dictionary" remain completely blank. It's as if we had an Enigma decryption device but only a limited understanding of a smattering of German words.

What's more, most gene words "mean"—that is, do—many things. It turns out nature loves puns; it is polysemic deep in its molecular essence. Nature also seems to love other wordplay, like the palindromic repeats—the PR in CRISPR—that were central to the tool's discovery. In addition, 926,535 "regulatory elements" (think of them as usage rules) are listed in what are misleadingly called "encyclopedias of DNA elements." Again, scientists are clueless about their meaning. We can crudely cut and paste with tools like CRISPR, but we are far from fluent in even the basics. Rather than having the "means to rewrite the code of life," as Isaacson suggests, it is truer to say we are like monkeys at molecular typewriters.

Isaacson stylishly mixes glancing prudence with gee-whiz gushing. He usefully reminds readers that the Human Genome Project's "grand medical breakthroughs that were predicted" haven't materialized, even for single-gene disorders. But he slips right back into hype-laden blather like "the great promise of gene editing is that it will transform medicine," giving humans the tools to "control evolution." Contrary to the impression created by the Human Genome Project's puffery (a prior case of pop science malpractice), many illnesses aren't—even in principle—addressable at the level of genes. Many conditions arise from complex combinations of behavioral, social, and contextual factors in which genes play roles but which it's hard to imagine will ever be "editable." Isaacson describes a real CRISPR treatment for sickle cell disease (priced at $1 million per treatment), but that sort of clean single-gene flaw is rare.

Such distinctions matter. The presumption that hard problems are on a continuous spectrum with easy cases has been dubbed the "first step fallacy": it's just a matter of taking more steps along the same path to crack the most complex cases. We see this fallacy often in techno-optimist circles. Now that artificial intelligence can classify cat pictures, some techies suppose we're on our way to solving the hardest patterning problems in every science. This sort of untethered-from-reality tech-boosterism has led to much misuse of talent, time, and treasure—and many disappointments.

Plainly stated, it's easier to see the absurdly wishful hand-wave-y thinking. The mind-bogglingly labyrinthine etiologies of diseases such as Alzheimer's or various cancers just aren't in the same conceptual category as single-gene illnesses (sickle cell, Tay-Sachs, Huntington's). Quoting, as Isaacson does, a venture capitalist saying, "We have in our crosshairs any disease with a genetic component. … We can go in and fix the error," without immediately throwing cold water on the claim amounts to more molecular malarkey. It's like reasoning that since bicycles and nuclear submarines are both technically vehicles, once we've cracked bike gears we'll soon be voyaging undersea. Nuclear subs aren't complicated bikes. And no amount of being great at gears will get you there.

Mischaracterizing such conceptual distinctions and complexities isn't just a harmless "zest for spinning," a phrase Isaacson uses to describe fact-stretching by the geneticist Eric Lander, founding director of the Broad Institute and now President Biden's science advisor. This hyping quickly spins out of control, with many negative effects, including channeling money away from boring but effective approaches to disease and giving investors, the public, and disease sufferers false hope.

Isaacson's metaphors do a lot of questionable work. He sees biochemistry's "molecules becoming the new microchips" and compares "digital coding to genetic coding." But obviously in computers, engineers build and understand every component; that is not nearly the case in molecular biology. Evolutionary scientist and physician Randolph

Nesse has called this fallacy "tacit creationism." It presumes a design-like evolutionary process of creating systems with fixed parts, like cogs or microchips, that have separable functions. In reality, life at the cellular level seethes with rapidly forming flash-mobs of varying molecular "parts" that operate in jostling crushes of a vast "Brownian storm" involving billions of proteins per cell.

More disturbing is the prominent role Isaacson gives to a biohacker jester, Josiah Zayner, who playfully chides the bureaucratic slowness of biomedical regulation. Isaacson is so captured by the genes-as-code metaphor and the idea that rebels "push humanity forward" that, "despite the dangers," he writes, society should "tap into the biological wisdom and innovation of crowds." But Zayner's declaration that genetic engineering "is no harder than computer engineering" should be disqualifying. And again, quoting him without correction is tantamount to pop science malpractice. Rather than a wiki-wisdom of crowds, we risk the malice of mobs. Consider computer viruses, which impose costs on all of us. (With one desktop computer, I spent more on antivirus software over the years than on the hardware.)

Doudna is much more cautious than Isaacson, and perhaps this characteristic doesn't fit his swaggering rebel mold. This difference may partly explain why she gets relatively few pages compared to the stars of his other genius biographies. Doudna is deeply troubled that CRISPR could become "a toolbox for future Frankensteins." She can "scarcely begin to conceive of all the ways [it] might be perverted." She describes a nightmare in which "Hitler with the face of a pig" asks her to explain CRISPR, which points to the perennial problem of any powerful technology: how does society ensure it is used only for good and not for nefarious purposes?

The standard answer is regulatory oversight and ethical checks and balances beyond the whims of the inventors. Doudna is "appalled" by the failure of the scientific community to self-regulate—resulting in the birth of gene-edited babies (the work of a rebel Chinese scientist who is currently serving a prison sentence). In his enthusiasm for Zayner and his approving quote of Steven Pinker saying bioethicists should "get out of the way," Isaacson makes clear his disdain for this kind of oversight.

In Isaacson's telling, the biohacker Zayner hopes to edit away the pain of bipolar anxiety that he fears he will pass on to his kids. Isaacson sagely intones that eventually we may isolate genes that predispose to psychiatric disorders. Here's the first step fallacy at work again. There are good reasons why many psychiatric conditions are unlikely ever to be genetically addressable. The broken-brain-due-to-bad-genes doctrine hasn't fared well. The World Health Organization, for instance, classifies depression as a biopsychosocial condition with nine main causal factors, only two of which are biological, and the rest behavioral and social. It's an unfounded assumption that "the biology" of every disease can be found at the genetic or molecular level. As neurogeneticist Kevin Mitchell pointed out on Twitter, for many "psychiatric conditions, [their] biology *emerges* at the level of neural systems" rather than directly from gene products.

In biology, words like "engineering" and "programming" perpetuate a deeply mistaken genes-are-like-code belief to which Silicon Valley entrepreneurs and many in the thinkerati seem highly susceptible. For instance, Elon Musk has said that "synthetic RNA (and DNA) … basically makes the solution to many diseases a software problem." Ray Kurzweil predicted we will "realistically model all biology" by 2030. Mark Zuckerberg and Priscilla Chan's foundation will "cure all diseases" by 2100. These Silicon Valley titans seem to express a combination of tacit creationism, the first step fallacy, and plain old hubris. They don't seem to have a handle on the tremendous intricacies involved in biology's level of complexity and its radical conceptual differences from human-built tech.

And although CRISPR technology is still in its infancy, Isaacson uses the tech-triumphalist trumpet to tug hard at our heartstrings, declaring it immoral not to use gene editing to reduce suffering. As a "moral principle," he writes, "everyone deserves freedom from genetic disease." Not only that: "Aren't we obligated to look after the welfare of our children and future humans in general?" In addition to treatments for disease, Isaacson weighs whether parents should be allowed to use gene editing to give their kids better lives by enhancing height, musculature, or intelligence.

He admirably expresses concerns about fairness and distribution; but, of course, we already have a technology that can enhance precisely those traits (and many more), thereby vastly reducing current human suffering. It's called food. A hundred and fifty million kids worldwide are stunted by malnutrition (as many as 30% of children in some poor nations). They suffer below-normal height and weight and lack schooling because we collectively choose to use resources for other purposes. I'll grant high-tech moral cheerleaders more credence when their

everything-is-getting-better gospel addresses such basic, non-cutting-edge necessities.

Isaacson endorses the idea that innovators need large financial incentives to ensure a continued supply of life-improving technologies; we could call this the need-greed innovation theory. He asserts that "the benefits of competition"—as facilitated by proprietary intellectual property—"are great," despite the "toxic effects" money can have on academic research. But his portrait of Doudna provides ample countertestimony to this idea.

An endearing aspect of Doudna is her unmercenary spirit. She felt "incredible disappointment and disgust" at the maneuvering of venture capitalists to monetize CRISPR, and Isaacson is very clear that she, like many scientists, isn't motivated by money. Isaacson describes an epic battle between the University of California and the Broad Institute over CRISPR patents that hindered research progress and was surely a vast misuse of prime cognitive resources. At the beginning of the pandemic, Doudna and her rivals in the CRISPR patent dispute immediately pooled their intellectual property on COVID-19 work.

The patent battle also highlights the fact that almost all important innovations in science and tech aren't solo genius eureka moments. They're community efforts with several teams circling the same ideas. Doudna's path is full of chance meetings, and her achievement rests on a great deal of collaboration. Who should get credit and financial gain from the vast collective effort of science? Even the idea of the Nobel Prize, which Doudna was awarded with her collaborator Emmanuelle Charpentier in 2020, embodies an impossible-to-justify hero worship.

Exactly because we need better-informed debates about all this, I'd recommend Isaacson's vast, vivacious book. *The Code Breaker* is a rousing epic narrated for our era's approved emotional palate, full of "passionate curiosity" and "fearless rebels." Isaacson says he relishes the "joy" of understanding the life sciences, and it shows. But let's work harder at the joyful details of using our tools, old and new, to edit and engineer away immediately avoidable—nongenetic—suffering.

***Jag Bhalla** is a writer and entrepreneur.*