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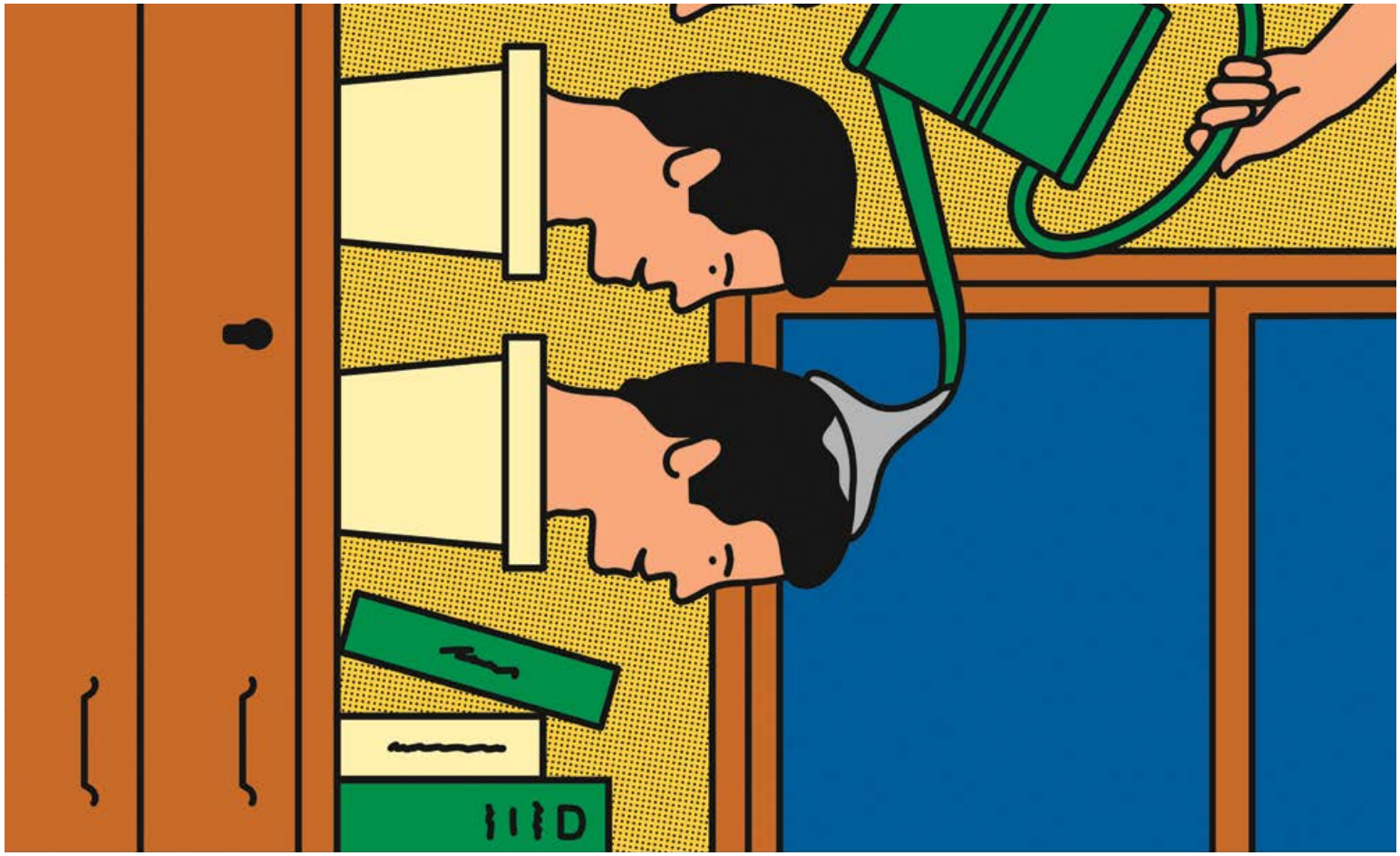

The Next Best Version of Me

Researchers want to synthesize an optimized human genome that can be stored indefinitely and grown decades from now. So I volunteered mine.

By
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GEORGE CHURCH TOWERS OVER MOST people. He has the long, gray beard of a wizard from Middle-earth, and his life's work—poking and prodding DNA and delving into the secrets of life—isn't all that far removed from a world where deep magic is real. The 63-year-old geneticist presides over one of the largest and best-funded academic biology labs in the world, headquartered on the second floor of the massive glass and steel New Research Building at Harvard Medical School. He also lends his name as an adviser or supporter to dozens of projects, consortiums, conferences, spinouts, and startups that share a mission to push the outer edge of everything, from biorobotics to bringing back the woolly mammoth. And on a steamy August morning last summer, he wants to talk to me about the outer edge of *my* life.

Church is one of the leaders of an initiative called the Genome Project-Write, or GP-Write, which is organizing the efforts of hundreds of scientists around the world who are working to synthesize the DNA of a variety of organisms. The group is still debating how far to go in synthesizing human DNA, but Church—standing in his office in a rumpled sport coat, behind the slender lectern he uses as a desk—says his lab has already made its own decision on the matter: "We want to synthesize modified versions of all the genes in the human genome in the next few years."

His plan is to design and build long chains of human DNA, not solely by cutting and pasting small fixes—a now-routine practice, thanks to recent technologies like Crispr that let scientists edit DNA cheaply and easily—but by rewriting critical stretches of chromosomes that can then be stitched together with a naturally occurring genome. If they succeed, it will be a breathtaking leap in ambition and complexity from the genomes of bacteria and yeast that scientists up until now have worked to synthesize. "What we're planning to do is far beyond Crispr," Church says. "It's the difference between editing a book and writing one."

In writing the book, Church hopes to bend the human narrative to his will. By replacing select nucleotides—the ACGTs of life, which are scattered throughout the chromosomes—and changing, say, a T to an A or a C to a G in a process called recoding, Church envisions being able to make cells resistant to viruses. "Like HIV and hepatitis B," he says.

"And the common cold?" I ask.

He nods yes, adding that they've already recoded bacteria to be virus-resistant. "It's in a paper we published in 2016," he says.

Church and others who are working to synthesize human DNA have created their own effort within GP-Write—the Human Genome Project-Write, or HGP-Write—and its prospects for success have biologists abuzz over the potential for treating diseases and for creating bioengineered cells and possibly even organs. Critics, though, are scratching their heads over the technical challenges, high costs, and practicality. Francis Collins, director of the National Institutes of Health, acknowledges that synthesizing a full human genome is feasible, but he doesn't quite see the point. "I think it's probably within the range of possibility, given enough time and money," he says, "but why would you want to do that? Technologies like Crispr are so much more accessible right now."

There are also the ethics of using a powerful new technology to muck around with life's basic coding. Theoretically, scientists could one day manufacture genomes, human or otherwise, almost as easily as writing code on a computer, transforming digital DNA on someone's laptop into living cells of, say, *Homo sapien*s. Mindful of the controversy, Church and his HGP-Write colleagues insist that minting people is not their goal, though the sheer audacity of making genome-scale changes to human DNA is enough to cause controversy. "People get upset if you put a gene from another species into something you eat," says Stanford bioethicist and legal scholar Henry Greely. "Now we're talking about a thorough rewriting of life? Hairs will stand on end. Hackles will be raised."

Raised hackles or not, Church and his team are forging ahead. "We want to start with a human Y," he says, referring to the male sex chromosome, which he explains has the fewest genes of a person's 23 chromosomes and is thus easier to build. And he doesn't want to synthesize just any Y chromosome. He and his team want to use the Y chromosome sequence from an actual person's genome: mine.

"Can you do that?" I stammer.

"Of course we can—with your permission," he says, reminding me that it would be easy to tap into my genome, since it was stored digitally in his lab's computers as part of an effort he launched in 2005 called the Personal Genome Project. (Disclosure: I've reported on Church for more than a decade, and he serves as one of 17 unpaid advisers to a small conference series I run called Arc Fusion.) The PGP has enlisted thousands of individuals to contribute their complete genomes to a public database open to researchers and everyone else, and I had donated my genome to the effort.

With my permission and a few clicks on his keyboard, Church can easily pull up a digital blueprint of my Y chromosome. Then scientists in his lab could build a synthetic replica, only with a difference: They would recode my sequence to be resistant to viruses. And if they're successful—and if they recoded the rest of my chromosomes and inserted them into a human cell, both huge *if*s—they could theoretically implant these "corrected" cells inside my body, where they would hopefully multiply, change how my body functions, and lower my risk for viral infection.

But we're getting ahead of ourselves. For now, Church merely wants to recode and synthesize my Y chromosome. "It'll be a little bit of you," he tells me, "that we'll keep in a freezer once we're finished." An optimized version of me that could one day be thawed out, in a dozen or a hundred or a thousand years. By then, Church explains, scientists might be able to further manipulate my genome. They could make me stronger or faster or maybe even smarter. They could possibly build an entirely new version of me. Who knows what will be feasible in the future?

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"I want to reiterate that we're not creating human babies," says Andrew Hessel. "That work will be coming for another generation."

SYNTHETIC BIOLOGY, A FIELD DEDICATED to understanding and reengineering the basic building blocks of life, has its roots in the early 1970s, when a team led by Stanford biochemist Paul Berg made key discoveries about how to cut and paste short DNA sequences from one organism (everything from bacteria to humans) into another (usually a bacterium). This practice allowed scientists to use a microbe's cell machinery to crank out proteins that in some cases became blockbuster drugs like Epogen, now commonly used to boost red-blood-cell production for those with anemia or on dialysis—or, um, in the Tour de France.

Larger-scale synthetic biology began to take hold in the early 2000s, when scientists began to synthesize complete viruses. In 2010, a team at the J. Craig Venter Institute created the first synthetic, self-replicating bacterial cell. But nothing so far has approached the ambitions of GP-Write or HGP-Write, which take their names from the original Human Genome Project, the massive endeavor that sequenced the 3 billion pairs of letters making up a human genome at a cost of $2.7 billion to US taxpayers. (A second, private effort led by geneticist Craig Venter was completed for significantly less money.) "We are looking at HGP-Write as the bookend" to the Human Genome Project, says geneticist Andrew Hessel, one of the founders of GP-Write and HGP-Write and a former researcher in the life-science unit of software giant Autodesk.

It was Hessel, a lean 54-year-old with a short, prickly beard, who first told me about this new human genome project three years ago when I visited him in his small, funky cottage near the Russian River in California's Sonoma County. Sipping red wine around a wood stove on a foggy night, Hessel talked about how he began his career in the late 1990s at Amgen analyzing data from Venter's private human genome effort. "Even as we were finishing HGP-Read," he says, using his and his colleagues' shorthand for the original Human Genome Project, "I was looking forward to seeing how we could start making things. Then I waited and waited, but nothing happened. It was a failure of imagination. The technology had reached a certain point, but no one was moving on it." He watched as Crispr and other gene-editing techniques emerged, but they didn't satisfy him.

In 2015, Hessel got more serious about a "write" project and asked Church to help lead the efforts that became GP-Write (and HGP-Write). Church insisted they also enlist another prominent synthetic biologist, New York University's Jef Boeke, as co-leader. The aims of the group range from facilitating the development of faster and cheaper technologies to developing an ethical framework for synthesizing life. They also have a ready answer to the question posed by Francis Collins and others about synthesizing human genomes—why do it? Hessel, Church, and company talk about the potential for large, genome-wide changes that could be used to develop viral-resistant cells , synthetic organs, and new drugs. They draw the line, however, at the prospect of activating a synthetic genome in germ-line cells that could alter the genes we pass down to our kids. "We're not creating human babies—we're just writing genomes," Hessel insists. "The real work to make a synthetic baby will be coming for another generation."

Last May, GP-Write held its first public meeting at the New York Genome Center. The two-day gathering attracted 250 scientists, ethicists, lawyers, educators, citizen scientists, artists, policymakers, and companies from 10 countries, including China, Japan, Britain, Canada, Singapore, and the United States. It featured sessions such as "Isothermal Amplification Array to Extend Synthetic Gene Sequence" and "Anticipating and Understanding Governance Systems."

The conference featured presentations about pilot projects that the organization was considering or endorsing. For instance, Columbia University's Harris Wang wants to bioengineer mammalian cells that can become nutrient factories churning out the critical amino acids and vitamins we otherwise have to consume through food. Another

With large-scale recoding, you have to wonder whether new and improved genomes would make us someone different altogether.

project, presented by June Medford of Colorado State University, aims to reengineer the genomes of plants so they can filter water or detect chemicals. At the meeting, she showed a slide of an airport gate encircled by explosive-detecting shrubbery.

The GP-Write movement had its latest big breakthrough last year, when Boeke's lab at NYU announced it had fully synthesized six of the 16 chromosomes that make up the genome of baker's yeast. Boeke plans to finish all 16 chromosomes by the end of this year. "We're setting out to untangle, streamline, and reorganize yeast's genetic blueprint," he says. "Once we've synthesized all 16 chromosomes, we plan to create a functioning yeast cell."

That will be a remarkable accomplishment, but given that yeast has only about one-quarter as many genes as people do, it's still not anything close to the complexity of synthesizing all or even part of a human genome. The longest of the 16 synthesized chromosomes in Boeke's yeast genome will measure around 1 million base pairs—base pairs being the doubling-up of genetic letters into pairs that run along each strand of DNA's double helix, like steps in a ladder. The Y chromosome comes in at 59 million base pairs, and that's among the shortest of a human's 23 chromosomes. Some scientists have estimated that writing an entire human genome, all 3 billion base pairs, could cost upwards of $3 billion, which is not only prohibitively expensive but probably unnecessary. "We don't need to rewrite everything" to make serious changes to the chromosome, Church explains. "Just those parts that are important."

IN 2002, AS PART OF WIRED'S EFFORT to explain and humanize the newfangled technology of genomic sequencing, I was one of the first people to be genetically sequenced. Back then, my genomic "read" seemed highly personal, claiming to reveal secrets about my health buried deep in my DNA. As part of my reporting, a San Diego–based company named Sequenom tested me for several hundred DNA markers associated with disease risk factors, ranging from Alzheimer's and hypertension to some forms of cancer. For instance, Sequenom's scientists found a mutation on my sixth chromosome that was later found to be associated with a slightly higher risk of heart attack. Like a lot of people who've had their genomes sequenced through services like 23andMe, I mentally stored this information under "good to know." Fifteen years (and zero heart attacks) later, as I contemplated my own personal HGP-Write project, I wondered how it would feel to know that a little piece of me was being partially copied and recoded to be new and improved.

After meeting with Church last summer, I sat down with his team in a conference room at Harvard's Wyss Institute for Biologically Inspired Engineering, a glass and steel marvel situated behind the Church lab's main building. The team included four researchers and 32-year-old Albanian postdoc Eriona Hysolli. With dark, braided hair and a serious demeanor, Hysolli walked me through how they'll build my Y chromosome.

Gene synthesis, Hysolli says, starts with the researchers looking up a subject's digital genetic sequence on a computer. On a glowing screen she shows me a segment of my sequence, which looks like this:

CGG CGA AGC TCT TCC TTC CTT
TGC ACT GAA AGC TGT AAC TCT
AAG TAT CAG TGT GAA ACG GGA
GAA AAC AGT AAA GGC AAC GTC
CAG GAT CGA GTG AAG CGA CCC
ATG AAC GCA TTC ATC GTG TGG
TCT CGC GAT CAG CGG CGC AAG
ATG GCT CTA GAG AAT CCC CGA

... and so on. Hysolli explains that, rather than synthesize every nucleotide in my Y chromosome, Church's team will focus on discrete genetic units, called codons, that determine what kind of amino acids (and, eventually, proteins) are produced by a cell. Each codon is made up of three nucleotides (ATG, for example, or TCC), and by swapping out certain nucleotides in the codons, Hysolli and her team hope to make genome-wide changes that would make a cell resistant to viruses. Once the targeted codons have been recoded, Hysolli will send this genetic blueprint to a company, Integrated DNA Technologies, which creates small, custom-made segments of actual DNA called oligonucleotides, or oligos. IDT will then freeze-dry the oligos and mail them back to Hysolli. She and her researchers will thaw

out the oligos and connect them into longer and longer sequences, with each new segment bringing them one step closer to a completed chromosome.

That's the plan, anyway, and it will take up to a year to complete the process. In the meantime, I ask Hysolli to provide a less ambitious demonstration of how writing DNA works. At first, she is reluctant to do something that she considers easy (for her). But she soon agrees, and we choose a segment of DNA on my sixth chromosome that contains the mutation revealed by my earlier genetic tests—the one that's associated with a modest risk of heart attack. To create a new and improved version of this gene fragment, Hysolli corrects the risky mutation on her computer. She also recodes this morsel of DNA to be resistant to viruses, just for good measure. Hysolli then orders the recoded DNA fragment from IDT, which arrives several days later.

Once they receive the fragment, the researchers clone it and drop it into the cytoplasm of *E. coli*, a well-known bacterium. Geneticists frequently do this to take advantage of *E. coli*'s rapid rate of reproduction. After several days, the *E. coli* have churned out enough of my altered chromosome that Hysolli sends me a picture of the bacteria in a petri dish containing these tiny bits of me. Not that I can actually see the nano-size flecks. But I can view a splattering of green glowing blobs inside the cell. The blobs are produced by a "fluorescent reporter gene," taken from a jellyfish, that is routinely used by scientists to tag genes in this way. The smudgy, brown-green soup of microbes speckled with glowing dots is a long way from being a recognizable version of me, but it did make me squirm a bit to think that one day I might be looking at a more complete version of my full genome in a petri dish, all gussied up.

The final step in creating this synthetic mini-me is to swap the repaired gene into cells to be stored. Not just any cells, though—scientists use my white blood cells to make what are called induced pluripotent stem cells, meaning that they can grow into any cell in the body. (This bioengineering is done by a Madison, Wisconsin, company called Cellular Dynamics International, which creates stem cells for pharmaceutical and academic outfits.) Someday these cells could be injected into my body in the hope of changing the way my body works, but right now, "getting edited cells in the body is super challenging," Hysolli says. "For many tissues, you can inject them directly and wait to see if a small percentage survive and thrive. Or you can inject blood stem cells intravenously and see if they home in on the bone marrow or the thymus." Until that technology matures, these doctored cells of mine will be frozen and stored, to be accessed by me or perhaps someone else in the future.

Church cautions that the technology behind genome-scale synthetic biology remains nascent, difficult, and expensive. GP-Write has yet to raise significant funds, though individual labs like Church and Boeke's have raised money from government agencies such as the National Science Foundation and Darpa, the Pentagon's R&D arm. For now, I'm not holding my breath that I'll get my recoded Y chromosome—or the tiny fix that Hysolli made on my chromosome six—implanted in me anytime soon. But they'll be sitting there in the deep freeze should the raft of ethical, technical, and safety issues ever get worked out.

I wonder, though, how this primal code that makes me who I am, for better or worse, might one day be used. I'm all for using the tech to develop new drugs or to make genome-wide DNA programming tweaks that might prevent diseases, if it's safe and has no unintended negative effects—a really big if. But if we push beyond the therapeutic barrier, I wonder how I'll feel if I or my children are enhanced to be smarter or stronger. Again, if it's safe, and if it actually works, I suspect many people would be eager for the upgrade, though you have to wonder whether such new and improved genomes—whether we use genome-scale recoding or other technologies like Crispr—would make us someone different altogether.

How this will play out in future years and decades is anyone's guess. But the tools are being forged right now that might make it possible to do far more than add a few improvements, says bioengineer Pam Silver of Harvard: "The driver is your imagination." She is part of the GP-Write project that is setting out to reengineer DNA to make amino acids that humans must otherwise consume through food. Her notion was echoed by geneticist Charles Cantor, a professor emeritus from Boston University who helped facilitate my original DNA "read" back in 2002 at Sequenom. Cantor thinks that scientists and ethicists are actually being too timid. "When I think of writing genomes," he says, "I like to think of the different genres people could write. Personally, I like fiction—coming up with totally novel genomes, like making people who are engineered to get their energy from photosynthesis, or a plant that can walk."

The fact that mainstream researchers are seriously thinking about cells that resist viruses and plants that might walk around makes it all the more critical that scientists like Church, Hessel, and Boeke—and younger researchers like Hysolli—publicly talk about all of this, and also spearhead groups like GP-Write to keep everything transparent and governed by standards as often as possible. "I think it's reassuring to the public that scientists are thinking about this, that they aren't just off doing mad-scientist kinds of stuff," says Nicole Lockhart, a program director at the NIH's Ethical, Legal, and Social Implications Research Program. Or as Hessel frames it: "We may not be able to stop bad guys from abusing this technology, but given that this technology is coming one way or another, it's always better to have this out in the open as much as we can."

During one of my final visits to her lab, I ask Hysolli what chromosome they will try next, once they've finished synthesizing my Y.

"We're not sure yet," she says. Perhaps one of the other small chromosomes, like 21 or 22. Church is encouraging her and her team to go ahead and try the X chromosome.

"That may be a bit much right now," Hysolli says, given that it has more than 10 times the number of genes and is much longer than the Y.

I gingerly ask her whose sequence they will use for these and other chromosomes to create the rest of their recoded synthetic human genome.

"We could use yours," she says, offering the barest hint of a smile before turning back to her work.