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Unlocking the Covid Code

By Jon Gertner

Edward Holmes was in Australia on a Saturday morning in early January 2020, talking on the phone with a Chinese scientist named Yong-Zhen Zhang who had just sequenced the genome of a novel pathogen that was infecting people in Wuhan. The two men — old friends — debated the results. "I knew we were looking at a respiratory virus," recalls Holmes, a virologist and professor at the University of Sydney. He also knew it looked dangerous.

Could he share the genetic code publicly? Holmes asked. Zhang was in China, on an airplane waiting for takeoff. He wanted to think it over for a minute. So Holmes waited. He heard a flight attendant urging Zhang to turn off his phone.

"OK," Zhang said at last. Almost immediately, Holmes posted the sequence on a website called Virological.org; then he linked to it on Twitter. Holmes knew that researchers around the world would instantly start unwinding the pathogen's code to try to find ways to defeat it.

From the moment the virus genome was first posted by Holmes, if you looked, you could find a genetic component in almost every aspect of our public-health responses to SARS-CoV-2. It's typically the case, for instance, that a pharmaceutical company needs samples of a virus to create a vaccine. But once the sequence was in the public realm, Moderna, an obscure biotech company in Cambridge, Mass., immediately began working with the National Institutes of Health on a plan. "They never had the virus on site at all; they really just used the sequence, and they viewed it as a software problem," Francis deSouza, the chief executive of Illumina, which makes the sequencer that Zhang used, told me with some amazement last summer, six months before the Moderna vaccine received an emergency-use authorization by the Food and Drug Administration. The virus's code also set the testing industry into motion. Only by analyzing characteristic aspects of the virus's genetic sequence could scientists create kits for the devices known as P.C.R. machines, which for decades have used genetic information to formulate fast diagnostic tests.

In the meantime, sequencing was put to use to track viral mutations — beginning with studies published in February 2020 demonstrating that the virus was spreading in the U.S. This kind of work falls within the realm of genomic epidemiology, or "gen epi," as those in the field tend to call it. Many of the insights date to the mid-1990s and a group of researchers in Oxford, England, Holmes among them. They perceived that following evolutionary changes in viruses that gain lasting mutations every 10 days (like the flu) or every 20 days (like Ebola) was inherently similar to — and, as we now know, inherently more useful than — following them in animals, where evolution might occur over a million years.

An early hurdle was the tedious nature of the work. The Oxford group had to analyze genetic markers through a slow and deliberate process that could provide insight into a few dozen characteristics of each new variant. It wasn't until the late 2000s that drastic improvements in genetic-sequencing machines, aided by huge leaps in computing power, allowed researchers to more easily and quickly read the complete genetic codes of viruses, as well as the genetic blueprint for humans, animals, plants and microbes.

In the sphere of public health, one of the first big breakthroughs enabled by faster genomic sequencing came in 2014, when a team at the Broad Institute of M.I.T. and Harvard began sequencing samples of the Ebola virus from infected victims during an outbreak in Africa. The work showed that, by contrasting genetic codes, hidden pathways of transmission could be identified and interrupted, with the potential for slowing (or even stopping) the spread of infection. It was one of the first real-world uses of what has come to be called genetic surveillance. A few years later, doctors toting portable genomic sequencers began tracking the Zika virus around Central and South America. Sequencers were getting better, faster and easier to use.

To many, the most familiar faces of this technology are clinical testing companies, which use sequencing machines to read portions of our genetic code (known as "panels" or "exomes") to investigate a few crucial genes, like those linked to a higher risk of breast cancer. But more profound promises of genome sequencing have been accumulating stealthily in recent years, in fields from personal health to cultural anthropology to environmental monitoring. Crispr, a technology reliant on sequencing, gives scientists the potential to repair disease-causing mutations in our genomes. "Liquid biopsies," in which a small amount of blood is analyzed for DNA markers, offer the prospect of cancer diagnoses long before symptoms appear. The Harvard geneticist George Church told me that one day sensors might "sip the air" so that a genomic app on our phones can tell us if there's a pathogen lurking in a room. Sequencing might even make it possible to store any kind of data we might want in DNA — such an archival system would, in theory, be so efficient and dense as to be able to hold the entire contents of the internet in a pillowcase.

Historians of science sometimes talk about new paradigms, or new modes of thought, that change our collective thinking about what is true or possible. But paradigms often evolve not just when new ideas displace existing ones, but when new tools allow us to do things — or to see things — that would have been impossible to consider earlier. The advent of commercial genome sequencing has recently, and credibly, been compared to the invention of the microscope, a claim that led me to wonder whether this new, still relatively obscure technology, humming away in well-equipped labs around the world, would prove to be the most important innovation of the 21st century. Already, in Church's estimation, "sequencing is 10 million times cheaper and 100,000 times higher quality than it was just a few years ago." If a new technological paradigm is arriving, bringing with it a future in which we constantly monitor the genetics of our bodies and everything around us, these sequencers — easy, quick, ubiquitous — are the machines taking us into that realm.

And unexpectedly, Covid-19 has proved to be the catalyst. “What the pandemic has done is accelerate the adoption of genomics into infectious disease by several years,” says deSouza, the Illumina chief executive. He also told me he believes that the pandemic has accelerated the adoption of genomics into society more broadly — suggesting that quietly, in the midst of chaos and a global catastrophe, the age of cheap, rapid sequencing has arrived.

One morning last August, after the pandemic’s first wave had ebbed on the East Coast, I visited the New York Genome Center in Lower Manhattan to observe the process of genetic sequencing. On that day, lab technicians were working on a slew of SARS-CoV-2 samples taken from patients at New Jersey’s Hackensack University Medical Center. Dina Manaa, a lab manager at the center, handed me a blue lab coat upon my arrival. “I’ll walk you through the entire process,” Manaa said, and over the next 20 minutes, we went up and down the lab’s aisles as she explained the work.

The sequencing of a virus, much like the sequencing of human DNA from a cheek swab or a drop of blood, is painstaking. Samples are moved along what is essentially an assembly line: “weighed” on exquisitely sensitive “scales” to check the mass of the specimen; bathed with chemical solutions known as reagents; tagged with a “bar code” of genetic material so each sample can be individually tracked. Most of the preparations, Manaa explained, are about checking the quality of the virus sample and then amplifying its genetic material — in effect, transforming a tiny and invisible amount of the coronavirus extracted from a swab into vast quantities of DNA, all in preparation for being read and analyzed by a device built to do exactly that.

In another lab, Manaa paused by a row of five sleek and identical new machines, the Illumina NovaSeq 6000 — or “Nova-*seeks*,” as they’re called. These were similar to the machines used in China to sequence the virus for the first time, six months before. The NovaSeqs are about the size of an office photocopier and have few distinguishing features, apart from a large touch-screen interface and a vent pipe that rises from the back of the device to the ceiling. Each machine costs roughly $1 million; there are about 1,000 of them in the world right now. At a nearby lab bench, a technician named Berrin Baysa was pipetting minuscule amounts of clear, virus-laden solutions from one tube to another and moving her mixtures into small, spinning centrifuges. After nearly two days of preparation, these were the final steps for the Hackensack samples. At last, Baysa combined the tiny cocktails she had made by pouring them together into something known as a flow-cell, a flat glass cartridge about the size of an iPhone, containing four hollow chambers. She then carefully popped the flow cell into a drawer slot in a NovaSeq 6000.

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“OK, keep your fingers crossed,” she said after punching some instructions into a touch-screen and then tapping “GO.” She held up both hands and crossed her own fingers.

For this particular task, it would take the machine two days to complete the readings, she said — meaning that at that point, the full genetic sequences of the virus would be ready for the "bioinformaticians," who would look for patterns and variants in the samples.

The NovaSeqs represent the culmination of about two decades of technological development that in large part began with the Human Genome Project, which was completed in 2003 and funded mainly by the National Institutes of Health. The project showed that the human genome — "nature's complete genetic blueprint for building a human being," as the N.I.H. describes it — is composed of a sequence of about three billion "base pairs." These are bonded chemicals coded as A, C, G and T, where A stands for adenine, C for cytosine, G for guanine and T for thymine. The chemical pairs are frequently grouped together on our chromosomes, in about 30,000 information-dense strings, or clumps. The clumps are our genes.

The Human Genome Project required 13 years of work and cost more than $3 billion. Jeffery Schloss, who for many years oversaw technology grants at the National Human Genome Research Institute, a division of the N.I.H., told me that in 2002, he attended a meeting to map out the future of sequencing. "This had been a massive effort, to sequence the human genome," Schloss recalls, "but we knew it was just the beginning of what we needed to do, which meant that sequencing had to change dramatically. And in the course of that meeting, some people brought up this crazy idea: What if you could sequence a big genome for a thousand dollars? What would that enable?"

Most of the scientists in Schloss's circle believed it might lead to profound revelations. By studying the genomes of a large population of, say, Alzheimer's patients, researchers might piece together how certain genes, or combinations of genes, could make someone more likely to become ill. In an even larger sweep, they might gain insights into the health or disease markers of entire population groups or countries. Sequencing might find uses beyond basic science — routine clinical scans for prenatal testing, say, or for genes known to increase the likelihood of certain cancers.

Schloss's office invested $220 million in various start-ups and ideas over a period of about 15 years. The ultimate goal was to help bring down the cost, and raise the speed, of whole-genome sequencing. Even if the $1,000 genome remained out of reach, perhaps a new generation of machines might come close. "It was really unclear how long it would take for any of those to get into commercialization," Schloss recalls. "They had to become commercially *successful*. It was all pretty uncertain." Indeed, many of the sequencing start-ups from the early 2000s ultimately failed in the marketplace. A few, however, were subsumed into the core technology of other firms. A company known as Solexa, for instance, developed ingenious ideas — known as "sequencing by synthesis" — that involved measuring genetic samples optically, with fluorescent dyes that illuminated elements of DNA in the samples. That company was ultimately bought by another firm — Illumina, which quickly became a leader in the industry.

As machines improved, the impact was felt mainly in university labs, which had relied on a process called Sanger sequencing, developed in the mid-1970s by the Nobel laureate Frederick

Sanger. This laborious technique, which involved running DNA samples through baths of electrically charged gels, was what the scientists at Oxford had depended upon in the mid-1990s; it was also what Dave O'Connor, a virologist at the University of Wisconsin, Madison, was using in the early 2000s, as he and his lab partner, Tom Friedrich, tracked virus mutations. "The H.I.V. genome has about 10,000 letters," O'Connor told me, which makes it simpler than the human genome (at three billion letters) or the SARS-CoV-2 genome (at about 30,000). "In an H.I.V. genome, when we first started doing it, we would be able to look at a couple hundred letters at a time." But O'Connor says his work changed with the advent of new sequencing machines. By around 2010, he and Friedrich could decode 500,000 letters in a day. A few years later, it was five million.

By 2015, the pace of improvement was breathtaking. "When I was a postdoctoral fellow, I actually worked in Fred Sanger's lab," Tom Maniatis, the head of the New York Genome Center, told me. "I had to sequence a piece of DNA that was about 35 base pairs, and it took me a year to do that. And now, you can do a genome, with three billion base pairs, overnight." Also astounding was the decrease in cost. Illumina achieved the $1,000 genome in 2014. Last summer, the company announced that its NovaSeq 6000 could sequence a whole human genome for $600; at the time, deSouza, Illumina's chief executive, told me that his company's path to a $100 genome would not entail a breakthrough, just incremental technical improvements. "At this point, there's no miracle that's required," he said. Several of Illumina's competitors — including BGI, a Chinese genomics company — have indicated that they will also soon achieve a $100 genome. Those in the industry whom I spoke with predicted that it may be only a year or two away.

These numbers don't fully explain what faster speeds and affordability might portend. But in health care, the prospect of a cheap whole-genome test, perhaps from birth, suggests a significant step closer to the realization of personalized medicines and lifestyle plans, tailored to our genetic strengths and vulnerabilities. "When that happens, that's probably going to be the most powerful and valuable clinical test you could have, because it's a lifetime record," Maniatis told me. Your complete genome doesn't change over the course of your life, so it needs to be sequenced only once. And Maniatis imagines that as new information is accumulated through clinical studies, your physician, armed with new research results, could revisit your genome and discover, say, when you're 35 that you have a mutation that's going be a problem when you're 50. "Really, that is not science fiction," he says. "That is, I'm personally certain, going to happen." In some respects, it has begun already, even amid a public-health crisis. In January, the New York Genome Center began a partnership with Weill-Cornell and NewYork-Presbyterian hospitals to conduct whole-genome sequences on thousands of patients. Olivier Elemento, a doctor who leads the initiative at Weill-Cornell, told me that the goal is to see how a whole-genome sequence — not merely the identification of a few genetic traits — could inform diagnosis and treatment. What is the best medication based on a patient's genome? What is the ideal dosage? "We're trying to address a very important question that's never been answered at this scale," Elemento explained: "What is the *utility* of whole-genome sequencing?" He said he believed that within one or two years, the study would lead to an answer.

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Some of the grandest hopes for sequencing have arisen from the notion that our genes are deterministic — and that by understanding our DNA’s code, we might limn our destiny. When an early reading of the human genome was unveiled in 2000, President Bill Clinton noted that we were getting a glimpse of “one of the most important, most wondrous maps ever produced by humankind.” But the map has often proved hard to read, its routes unclear. The past 20 years have demonstrated that inherited genes are just one aspect of a confounding system that’s not easily interpreted. The progress of using gene therapy to treat diseases, for instance, has been halting; it wasn’t until last year that physicians had a resounding success with a treatment on several patients with heritable genes for sickle-cell anemia. In the meantime, scientists have come to realize something else: A complex overlay of environmental and lifestyle factors, as well as our microbiomes, appear to have interconnected effects on health, development and behavior.

And yet, in the course of the past year, some of the extraordinary hopes for genomic sequencing did come true, but for an unexpected reason. During the summer and fall, I spoke frequently with executives at Illumina, as well as its competitor in Britain, Oxford Nanopore. It was clear that the pandemic had meant a startling interruption in their business, but at each company the top executives perceived the situation as an opportunity — the first pandemic in history in which genomic sequencing would inform our decisions and actions in real time.

From the start, the gen-epi community understood that the SARS-CoV-2 virus would form new variants every few weeks as it reproduced and spread; it soon became clear that it could develop one or more alterations (or mutations) at a time in the genome’s 30,000 base letters. Because of this insight, on Jan. 19, 2020, just over a week after the virus code was released to the world, scientists could look at 12 complete virus genomes shared from China and conclude that the fact that they were nearly identical meant that those 12 people had been infected around the same time and were almost certainly infecting one another. “That was something where the genomic epidemiology could help us to say, loudly, that human transmission was rampant, when it wasn’t really being acknowledged as it should have been,” Trevor Bedford, a scientist at the Fred Hutchinson Cancer Research Center, told me.

When Bedford’s lab began studying viral genomes in Seattle, he could go a step further. By late February, he concluded that new cases he was seeing were not just being imported to the U.S. from China. Based on observations of local mutations — two strains found six weeks apart looked too similar to be a coincidence — community transmission was happening here. On Feb. 29, Bedford put up a Twitter post that noted, chillingly, “I believe we’re facing an already substantial outbreak in Washington State that was not detected until now.” His proof was in the code.

Bedford's lab was one of many around the world that began tracking the virus's evolution and sharing it in global databases. In the meantime, gen-epi researchers used sequencing for local experiments too. In the spring of 2020, a team of British scientists compared virus sequences sampled from ill patients at a single hospital to see if their infections came from one another or from elsewhere. "We were able to generate data that were useful in real time," Esteé Torok, an academic physician at the University of Cambridge who helped lead the research, told me. "And in an ideal world, you could do that every day." In other words, sequencing had advanced from a few years ago, when scientists might publish papers a year after an outbreak, to the point that genetic epidemiologists could compare mutations in a specific location in order to be able to raise alarms — *We have community spread! Patients on Floor 3 are transmitting to Floor 5!* — and act immediately.

To watch the pandemic unfold from the perspective of those working in the field of genomics was to see both the astounding power of new sequencing tools and the catastrophic failure of the American public-health system to take full advantage of them. At the end of July, the National Academy of Sciences released a report noting that advances in genomic sequencing could enable our ability "to break or delay virus transmission to reduce morbidity and mortality." And yet the report scathingly noted that sequencing endeavors for the coronavirus were "patchy, typically passive, reactive, uncoordinated and underfunded." Every scientist I spoke with understood that the virus could evolve into dangerous new variants; it was many months before one in particular, known as B.1.1.7, emerged and demonstrated that it was more transmissible and most likely more deadly. Researchers were similarly worried that our sequencing efforts to track the pathways of infection — unlike more serious and government-supported efforts in Britain or Australia — were flailing.

One of the Biden administration's approaches to slowing the pandemic has been to invest $200 million in sequencing virus samples from those who test positive. With the recent approval of the $1.9 trillion American Rescue Plan, a further $1.75 billion will be allocated to the Centers for Disease Control and Prevention to support genomic sequencing and disease surveillance.
In late January, the C.D.C. began disbursing money to public-health laboratories around the country to bolster the sequencing work already being done at academic labs. But the effort was starting from a low baseline. One calculation in The Washington Post noted that the United States had ranked 38th globally in terms of employing sequencing during the pandemic; as of mid-February, the U.S. was still trying to catch up to many European and Asian countries. And it therefore couldn't be said that new or dangerous variants weren't landing on our shores or emerging here afresh. What *could* be said is that we were unable to know.

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One day at the New York Genome Center, a researcher named Neville Sanjana told me that he thinks of genetic sequencers not as a typical invention but as a kind of "platform technology." The phrase resonates among those who study innovation. Such technological leaps are rare. They

represent breakthroughs that give rise to “platforms” — cellphones, say, or web browsers — that in time revolutionize markets and society.

The immense value of a platform innovation is related to how it can be adapted for a range of uses that are unforeseen at its inception. It can be like a toolbox, waiting at the back of a closet. What happened with sequencing during the pandemic serves as a good example. Another is Sanjana’s work on new Crispr technologies, which he uses to modify or repair strings of DNA to better understand the genetic basis of human disease. Twenty years ago, when officials at the N.I.H. talked about investing in the future of sequencing, altering the human, plant or animal genome on a regular basis was not something they could have predicted. But Crispr requires Sanjana to constantly evaluate his editing by using sequencers — usually a desktop Illumina model, in his case — to check the results. “It would be impossible to do these experiments otherwise,” he says.

It has been the case historically that platform innovations don’t merely create new applications. They create new industries. And while countless genomics companies have already sprung up, for now just four companies run most of the sequencing analyses in the world. These are Illumina and Pacific Biosciences, based in the United States; Oxford Nanopore Technologies, based in Britain; and China’s BGI Group.

According to the Federal Trade Commission, Illumina controls roughly 90 percent of the market for sequencing machines in the U.S., and by the company’s own assessment, it compiles 80 percent of the genomic information that exists in the world in a given year. It is sometimes described as the Google of the genomics business, not only because of its huge market share but also because of its products’ ability to “search” our complete genetic makeup. In short, it dominates the business. Last year, the firm took in over $3 billion in revenue and about $650 million in net income. In its hunger for expansion, the company has recently made a run of acquisitions. In late September, for example, Illumina announced that it intended to acquire, for $8 billion, a biotech company called Grail, which has created a genomic test that runs on an Illumina sequencer and that an early study suggests can successfully detect more than 50 types of cancers from a small sample of blood. On a recent corporate earnings call, deSouza called Grail and early cancer detection “by far the largest clinical application of genomics we’re likely to see over the next decade or two.”

As the pandemic unfolded, I spoke often to genomics executives about which industries could be transformed by their technologies and how their machines would be deployed in the years to come. One model for the future was built around the strengths of Illumina — big machines like the NovaSeq, with an extraordinary capacity for sequencing, housed in central testing labs (as they are now) and run by specialists. But a very different set of ideas emerges from one of Illumina’s main competitors, Oxford Nanopore. Oxford’s sequencers involve a technology that is electronic rather than optical; it is based on the concept of moving a sample of DNA through tiny holes — nanopores — in a membrane. The device measures how genetic material (extracted from a sample of blood, say) reacts to an electric current during the process, and it registers the letter sequence — A, G, C, T — accordingly. One distinctive feature is that a nanopore device can

read longer threads of DNA than an Illumina device, which can be helpful for some applications. It can also give readouts in real time.

Yet the biggest difference may be its portability. In 2015, Oxford Nanopore began selling a sampling and sequencing gadget called the Minion (pronounced MIN-eye-on) for $1,000. It is smaller than a small iPhone. The chief executive of Oxford Nanopore, Gordon Sanghera, told me he sees his company's tool as enabling a future in which sequencing insights can be derived during every minute of every day. Inspection officers working in meatpacking plants would get results about pathogenic infection in minutes; surveyors doing environmental monitoring or wastewater analysis can already do the same. Your dentist might one day do a check of your oral microbiome during a regular visit, or your oncologist might sequence your blood once a month to see if you're still in remission. A transplantation specialist might even check, on the spot, about the genomic compatibility of an organ donation. "The company's ethos," Sanghera says, "is the analysis of anything, by anyone, anywhere." Indeed, there happens to be a Minion on the International Space Station right now.

The technology, compared with Illumina's, is considered by most scientists I spoke with to be less accurate, but it has advantages beyond those that Sanghera mentioned. It was the Minion that enabled scientists to test for diseases like Zika without any infrastructure beyond a laptop; more recently, it's what allowed Esteé Torok and other researchers in Britain to track viral mutations in real time in a hospital. "That ability to do sequencing in the field, even in rural Africa, has opened up possibilities that were never previously even envisioned," Eric Green, who runs the National Human Genome Research Institute, part of the N.I.H., told me recently.
Bringing the equivalent of an iPhone into genomics may not effect a revolution overnight. Sanghera doesn't imagine that big central testing labs, or Illumina, could fade away anytime soon; indeed, his own company markets a line of large sequencers for big labs, too. And for sure, related technologies can coexist, much like cloud computing and desktop computing, especially if they solve different problems. For now, Sanghera regards the coronavirus, and the surveillance efforts in Britain and the U.S. that are increasing demand for his company's products, as hastening the culture's genomic transition. He said he sees no obstacle to a $100 whole human-genome sequence in the near future. His company, he told me, is also working with a new chip that may eventually bring down the cost to $10.

It seems beyond debate that the pandemic has demonstrated that we can benefit from genomic sequences even before we fully unravel all their mysteries. We can use them as a sort of global alarm system, for instance, much as they were used by Eddie Holmes and Yong-Zhen Zhang when they shared the SARS-CoV-2 sequence in January 2020. As it happens, there are a variety of different surveillance efforts underway, some driven by health agencies and others by academics, that would go much further than simply posting a sequence on a website — efforts that would share critical public-health information faster and, more broadly, might be useful for another new coronavirus, a deadly influenza strain or even a bioterror attack.
Pardis Sabeti, a geneticist at Harvard, told me that last May she received a philanthropic grant to help develop and deploy a pandemic "pre-emption" network called Sentinel. "We've always aimed for that ability to do surveillance," she told me, adding that the goal of Sentinel would be

to use genomic technologies everywhere — in rural clinics in Europe, villages in Africa, cities in China — to detect familiar pathogens within a single day of their appearance and novel pathogens within a week. The system would then race to share the data, via mobile networks, with health workers and communities so as to elicit a rapid response: travel restrictions, quarantines, medicine. Anything necessary to break chains of transmission. With a virus that spreads exponentially, a day could matter. A week could mean the difference between a small but deadly outbreak and a global cataclysm. (The time between the first case of Covid-19 and the release of the sequence of the virus was most likely about two months.)

As successive waves of the pandemic washed over the world, I noticed that the buzzword at the sequencing companies also became "surveillance." For the most part, it meant tracking new variants and using sequencing codes to help reveal paths and patterns of transmission. Yet surveillance sometimes seemed a flexible concept, given that Illumina and Oxford Nanopore were selling flexible machines. Surveillance could mean the search for the next novel virus in Asia or even early cancer detection in our bodies. And it sometimes meant mass testing too. Last year, both deSouza and Sanghera successfully adapted their companies' machines to do clinical diagnostic tests for the coronavirus; the goal was to step in and help increase global testing capacity at a moment when many medical facilities were overwhelmed by the demand.

In many respects, a genetic sequencer is over-engineered for the task of simply testing for a virus. A P.C.R. machine is faster, cheaper and less complex. And yet there are potential advantages to the sequencer. Illumina eventually won emergency approval from the Food and Drug Administration for a diagnostic test for the NovaSeq that can run about 3,000 swab samples, simultaneously, over the course of 12 hours. Thus, a single machine could do 6,000 coronavirus tests per day. Two hundred NovaSeqs could do more than a million. In addition to this immense capacity, it's viable to test for the virus and sequence the virus at the same time: An analysis run on a sequencer could inform patients whether they have the virus, and the anonymized sequencing data on positive samples could give public-health agencies a huge amount of epidemiology data for use in tracking variants. "I can envision a world where diagnosis and sequencing are kind of one and the same," Bronwyn MacInnis, who directs pathogen genomic surveillance at the Broad Institute, told me. "We're not there yet, but we're not a million miles off, either."

Last summer, a few big clinical laboratories, notably Ginkgo Bioworks in Boston, began plans to roll out tests for Illumina sequencers, pending authorization from the F.D.A. Ginkgo, with help from investments from Illumina, as well as a grant from the N.I.H., began building a huge new laboratory next to its current one, where the company would install 10 NovaSeqs. "After we get the big facility built, that's when we'd be trying to hit 100,000 tests a day," Jason Kelly, Ginkgo's chief executive, told me at the time. It was technically possible to sequence many of the positive coronavirus samples, too, he said.

When I asked Kelly what he would do if his capacity goes unused, he didn't seem concerned. He doubted his sequencers would be idle. "By betting on sequencers as our Covid response," he remarked, "we get flexibility for what you can use this for later." After the pandemic, in other

words, there will still be new strains of flu and other viruses to code. There will be a backlog of sequencing work for cancer and prenatal health and rare genetic diseases. There will be an ongoing surveillance effort for SARS-CoV-2 variants. An even bigger job, moreover, involves a continuing project to sequence untold strains of microbes, a project that Ginkgo has been involved with in search of new pharmaceuticals. “I think of this as like building fiber in the late 1990s, for the internet,” Kelly said. “Back then, we laid down huge amounts of fiber, then everything crashed.”

But it turned out that a decade after the dot-com crash, optical fiber was essential for the expanding traffic of the web. And what Kelly seemed to be saying, I later realized, was that he would expand his lab because sequencing had to be the future, in all kinds of different ways. There was no going back.

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