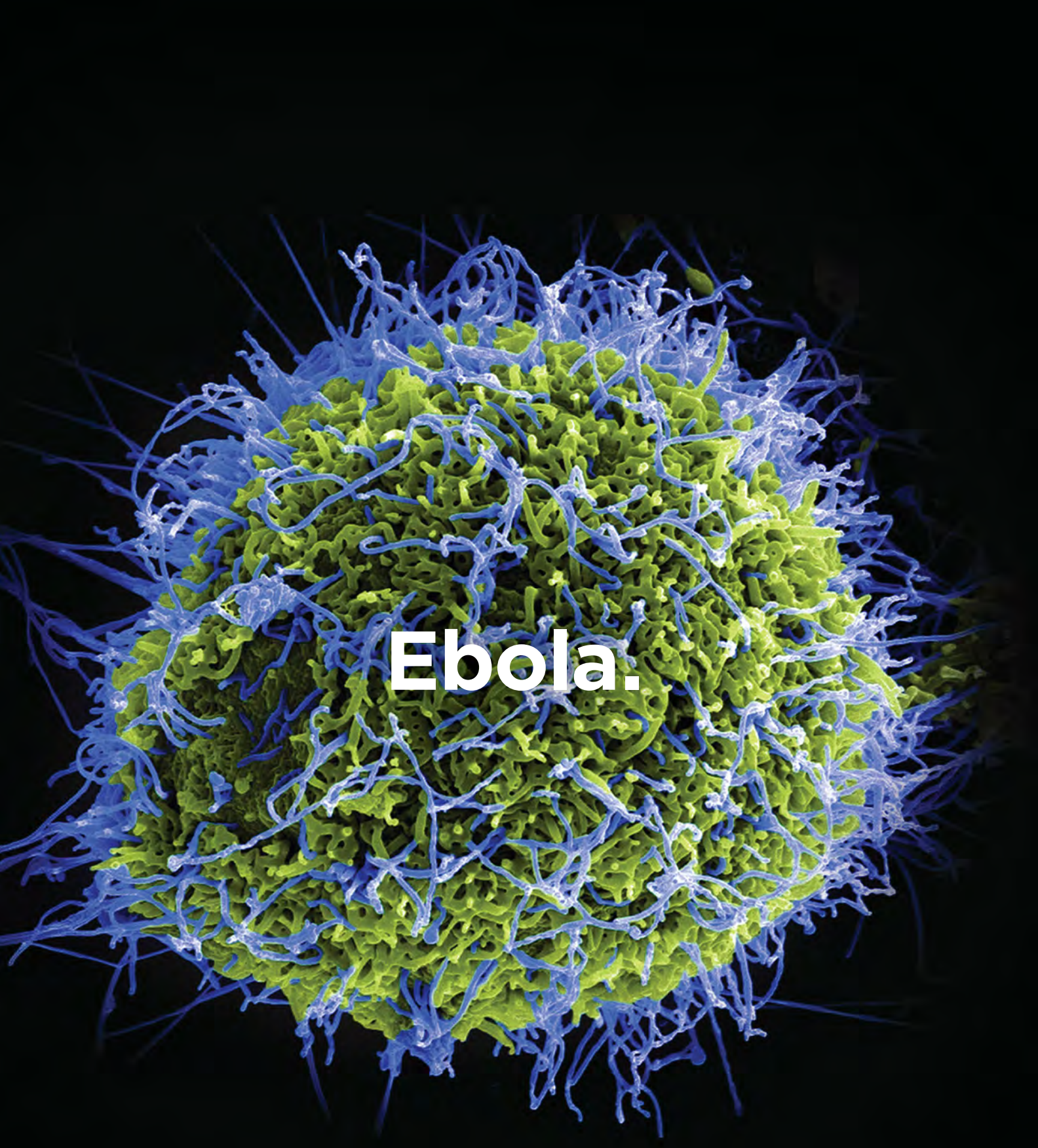


HOW GOVERNMENT AND PRIVATE-SECTOR DETECTIVES ARE

The Back Story.

USING NEW TECHNOLOGY TO STAMP OUT EBOLA AT ITS SOURCE.

By Christopher R. O'Dea

A high-stakes detective mission is taking shape in Western Africa, pitting some of the world's most sophisticated genetic technology against the Ebola virus. The race is on to crack the code of a pathogen that has proven to be one of the most lethal diseases facing humans since it emerged from the banks of the Ebola River in the continent's central jungle in 1976. In 2014, the U.S. Agency for International Development (U.S.A.I.D.) funded a public-private partnership to provide genetic sequencers from San Diego–based Illumina Inc. to clinics in Western Africa established by Dr. Pardis Sabeti of the Broad Institute of Harvard and M.I.T. in Cambridge, Mass. The Broad Institute is one of the leading genomic research centers in the world, and Illumina designs and manufactures some of the world's fastest and most advanced gene-sequencing machines. The aim is to give researchers the edge in tracking this deadly and rapidly mutating virus.

The Iranian-born Sabeti is a computational biologist, using advanced mathematics and massive computing power to read the genetic "instruction manuals" that determine how viruses adapt over time as they move through a human population. She has developed tools to determine how long gene mutations have been present in a population, which provides clues about how the disease is adapting to host organisms—and how humans develop defenses against the virus. Sabeti and her team believe Ebola may have been circulating in humans for longer than is commonly believed, and that studying the genetic structure of Ebola virus samples from infected people will help develop diagnostic tests and treatments.

"**Genomic surveillance**—that is, tracking how a virus is moving and changing in real time—is critically important," said Sabeti. The stakes couldn't be higher. The World Health Organization announced on Dec. 29, 2014, that Ebola continued to spread, with nearly 400 new cases reported in just four days. All told, W.H.O. reported that Ebola had infected 20,081 people and killed 7,842 by year-end, with Sierra Leone supplanting Liberia as the country hardest hit by the virus.

The Broad Institute–Illumina partnership will create an early warning system that "changes our ability to pick up mutations," said Dennis Carroll, director of the U.S.A.I.D. Avian Influenza and Other Emerging Threats Unit. "What they are going to do, we see as critical." The agency is providing financial support to the partnership, which will build on Broad's existing network in Africa. "They have a history of working in the region, and that meant we could do this quickly," Carroll said.

Time is tight. This Ebola outbreak is testing the limit of researchers' best efforts to stay ahead of the spreading pathogen. Using Illumina's top-end sequencers at the Broad Institute, Sabeti and her team studied genetic samples of the virus obtained from 78 individuals infected early in the outbreak—and found that the virus is changing two to three times as rapidly as in previous outbreaks, compounding the chances that it could become more virulent or more easily transmissible. The results were published in the journal *Science* in September 2014, and Sabeti released the genetic dataset for use by all researchers. Sabeti's team concluded that the rate of mutations "suggests that continued progression of this epidemic could afford an opportunity for viral adaptation, underscoring the need for rapid containment."

The ability to conduct genomic surveillance will bol-

The race is on to crack the code of a pathogen that has proven to be one of the most lethal diseases facing humans since it emerged from the banks of the Ebola River in the continent's central jungle in 1976.

A mother and child in a closed primary school now used as an Ebola isolation ward in Liberia.

JOHN MOORE / GETTY IMAGES

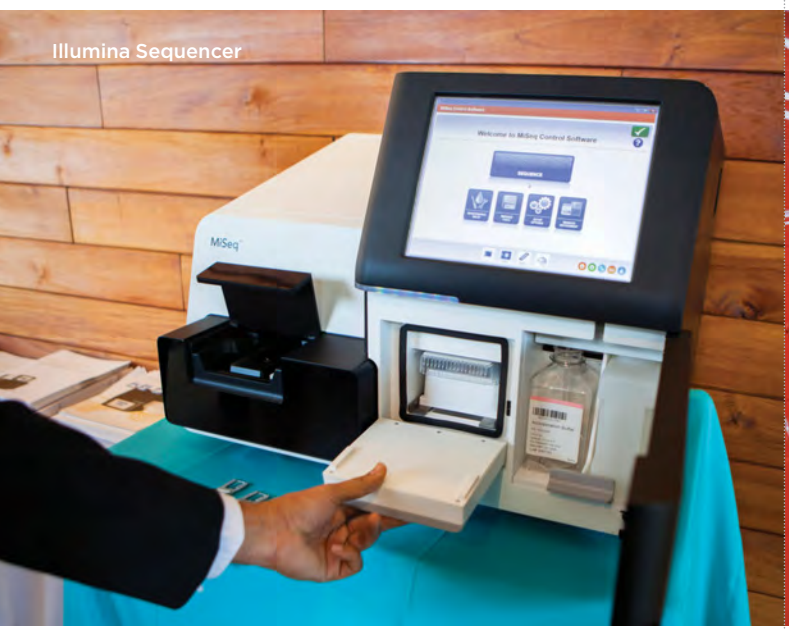
ster medical personnel struggling to contain the virus. "The sheer magnitude is unprecedented," said Carroll. "We'd never witnessed this kind of human-to-human transmission dynamic before at this scale." Because previous Ebola outbreaks in Central Africa were mostly confined to isolated rural communities, "this is a virus that's never been introduced to a population of more than a few hundred," he said. "That's very different than controlling something that's entered a population that's highly mobile and urbanized."

Sabeti's West African network is eager to deploy the new genetic defenses against Ebola. "We're excited to soon get the MiSeq on the ground," said Christian Happi, a professor at Redeemer's University in Nigeria, referring to Illumina's state-of-the-art desktop gene sequencer. Sequencing and patient-monitoring facilities will be created first in Liberia, Nigeria, Senegal and Sierra Leone, and then in other West African countries. Those centers will serve as hubs for the deployment of mobile laboratories to remote districts, extending the front line against the virus in an effort to detect infections earlier. The sequencers will "produce genomic information critical in the global response," he said. Happi's lab, which played a key role in early Ebola diagnosis, is also set to sequence the 20 confirmed and suspected cases from the Nigerian outbreak of the disease that was declared over in October 2014.

Like any perpetrator, Ebola has a modus operandi, controlled by its DNA. Sequencing allows investigators to read the virus's "instruction manual" by determining the unique order of the four building blocks of genetic matter—adenine, guanine, cytosine and thymine—encoded within its DNA molecules. There are several sequencing methods, but Illumina's technology allows

Illumina sequencers paint DNA molecules mounted on a slide with a solution in which each of the building blocks is labeled with a different color. The building blocks attach themselves to sites on the DNA molecule where a camera records the fluorescent sequence, revealing the genetic instructions.

researchers to unlock the code faster than other techniques operate—and the faster researchers can "read" the virus's instruction set, the faster they can take steps to counteract its effects. Illumina sequencers paint DNA molecules mounted on a slide with a solution in which each of the building blocks is labeled with a different color. The building blocks attach themselves to sites on the DNA molecule where a camera records the fluorescent sequence, revealing the genetic instructions. Illumina's method provides researchers with enormous capacity by separating the color-coding and image capture into two steps, allowing the machine to process more samples in a given time period.



Illumina Sequencer

While the MiSeq sequencers being sent to Africa don't need to be cleared by the U.S. Food and Drug Administration, which regulates devices like gene sequencers, the F.D.A. gives the technology high marks. "We think that it is a well-controlled, great instrument to be sending to Africa," said Alberto Gutierrez, director of the F.D.A.'s Office of In Vitro Diagnostics and Radiological Health. In late 2013, the F.D.A. issued a novel approval for a clinical test for cystic fibrosis to be performed on MiSeqs manufactured under tight rules for the U.S. market. "We have seen data in terms of the analytical performance of the MiSeq, and we actually think that instrument has very good controls," Gutierrez said. As for the research team in the new partnership, he added, "We've worked with the Broad group, so I'm sure that what is being done there is scientifically very sound."

Sabeti has been training medical and scientific colleagues in Nigeria, Senegal and Sierra Leone to use sequencing technologies for several years. Through support from the National Institutes of Health and the World Bank, 11 researchers from Nigeria and Senegal completed an advanced training program in genomics at the Broad Institute in 2014, which included the use of Illumina technology. African medical personnel will now be equipped "to provide real-time information about the circulation and mutation of Ebola virus strains," Sabeti said.

The partnership against Ebola highlights the potential for genetic technology to give medical personnel a powerful weapon against diseases. F.D.A. Commissioner Margaret Hamburg believes genetic medicine has a bright future. "Genomics and next-generation sequencing are very important components of what is already happening and what will happen in the future," she said in an online interview with Eric Topol, chief academic officer at Scripps Health and editor-

Dr. Pardis Sabeti of the Broad Institute of Harvard and M.I.T. in Cambridge, Mass., is a computational biologist using massive computing power to reveal how viruses like Ebola adapt as they move through the human population.

in-chief of Medscape, an online health site. "We support the notion of consumers and their health care providers having access to this kind of information," she said, "but we feel strongly—whether it is a genetic test or any other kind of a diagnostic test—that the test be accurate and reliable."

With U.S. government agencies backing genetic technology at home—and funding training and deployment of the tools against Ebola—it's only a matter of time before gene-based medicine becomes prevalent in U.S. medical practice. Working effectively with regulators will be essential for companies to succeed in genomic medicine—and competition is also ratcheting up to a new scientific level.

Illumina has set up its own gene-tech incubator with Yuri Milner, a Russian billionaire and technology investor. One of the aims of the incubator is to turn smartphones into what Illumina's chief technology officer Mostafa Ronaghi calls "molecular stethoscopes." Ronaghi told a conference in Brussels that the company is exploring electrical and optical technology that would allow a silicon chip to read genetic information and transmit the data for diagnosis. Although technical hurdles remain, he's confident smartphone genomics will fundamentally alter health care. "We will not need a primary doctor in the future," Ronaghi said. Consumers will be able to get tested at home or in a clinic, then go directly to a specialist. "I believe it will happen in five to seven years," he said.

While it may be some time before smartphones replace primary care doctors in the U.S., one thing is clear—genetic medicine is here to stay. In a comment in the *Journal of the American Medical Association,* Patricia Zettler of the Center for Law and the Biosciences at Stanford University summarized the state of play: "The era of widespread, clinical use of DNA sequencing rapidly approaches," she said.

In Western Africa, said former U.S.A.I.D. Administrator Rajiv Shah, it's already here. "By partnering with experts from the Broad Institute and Illumina, we can give health workers the tools they need to win the fight against Ebola."

CORBIS • BROAD INSTITUTE

The partnership against Ebola highlights the potential for genetic technology to give medical personnel a powerful weapon against diseases.