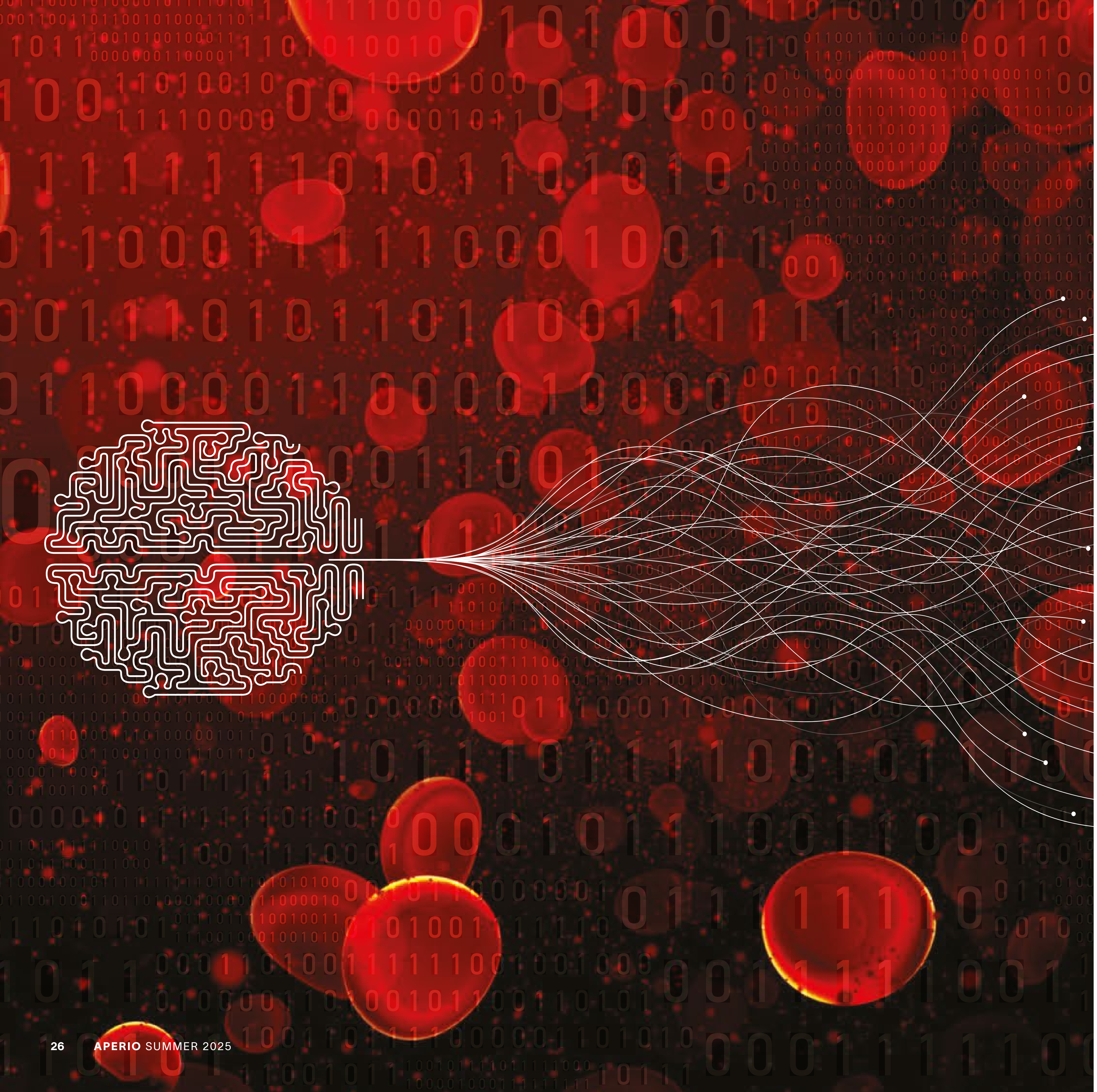


By Wendy Glauser
Photographs by Mark Rocha

AN INFECTIOUS ENTHUSIASM FOR AI

THE KARIUS TEST USES AI TO BRING SPEED AND PRECISION TO THE DIAGNOSIS OF INFECTIOUS DISEASE

The treatment of infectious disease often becomes a race against time. Doctors desperately order test after test to determine the cause of a patient's infection. They ask about recent travel destinations or interactions with animals, trying to narrow down possible pathogen exposures. Meanwhile, the patient's condition continues to deteriorate.

Can artificial intelligence change this scenario? After all, AI is transforming clinical decision-making, personalized disease treatment, imaging analysis, drug development and much more. What if it could also transform the way doctors approach infectious disease?

It turns out, thanks to the trailblazing work of Sivan Bercovici and his team, it already is.

Bercovici, a computer scientist and former Azrieli Graduate Studies Fellow, is leading the team pioneering a new AI-enabled test that screens samples for more than 1,000 human pathogens all at once. Known as the Karius Test, the technology can help physicians reduce the time it takes to diagnose patients with an infection. Published literature by a growing community of healthcare providers, as well as by Bercovici and his colleagues, have demonstrated its diagnostic value where other tests have failed. More than 500 U.S. hospitals already use the test, with the Karius corporate facility in Redwood City, California, having processed nearly 90,000 cases so far.

"When cells in your body die, DNA is spilled into the bloodstream," says Bercovici. This also happens when bacteria, fungi, parasites or viruses die — even when an infection is worsening, as some of these infecting cells still break down and release their DNA. "The test we've developed, offered as an approved laboratory developed test service, is the only approved test that can detect and interpret that signal."

For the last 20 years, Bercovici has been studying the intersection between human health and machine learning. During his PhD work at Technion–Israel Institute of Technology, he focused on developing methods to discover genes that contribute to diseases, including prostate cancer, multiple sclerosis and end-stage kidney disease. In one example, using an AI program that analyzed genetic information taken from hundreds of patients, Bercovici helped pinpoint mutations in a single gene that explained why African Americans have a four-fold risk of end-stage kidney disease compared to Americans of European descent.

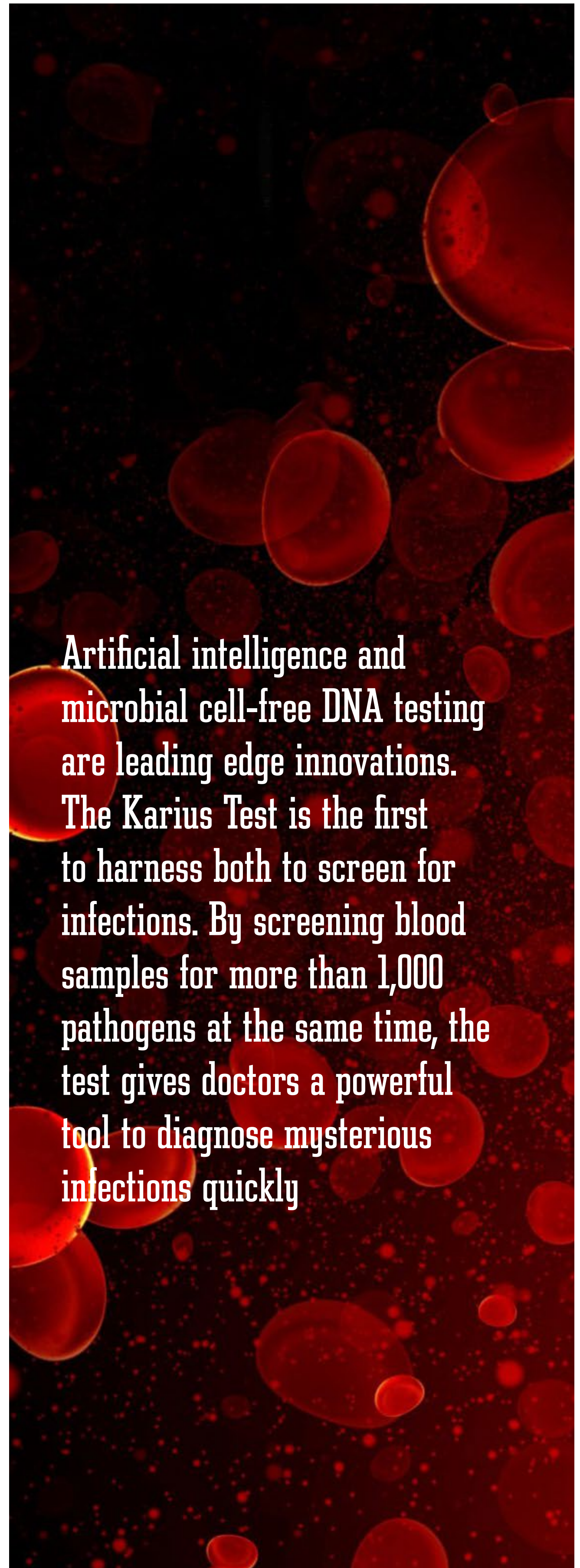
"Some 15 years later, there are major practical diagnostic and therapeutic advances that have come out of this work," says Karl Skorecki, professor emeritus and former dean of the Azrieli Faculty of Medicine at Bar-Ilan University, with whom Bercovici collaborated on kidney disease research.

After completing his PhD, Bercovici continued to apply AI to genetic analysis in his postdoctoral work, and, later, as a senior research scientist at Stanford University. "One thing about hanging out at Stanford is that you get to see really exciting stuff that is very far from commercialization," says Bercovici. "It's a glimpse into the future."

In 2016, Bercovici was hired as chief technology officer for Karius, a start-up enterprise with big plans to transform infectious disease care. The opportunity allowed him to continue his research from his time as a graduate student into using AI to analyze microbial cell-free DNA, just at an accelerated pace. In his role, he leads the development of the software and machine learning algorithms behind the Karius Test, algorithms that he and his team continually test and tweak to improve accuracy.

Bercovici credits his Azrieli Foundation–supported graduate research and postdoctoral work at Stanford as crucial to his success at Karius, where he oversees a team of more than 40 engineers, statisticians, software engineers and others. At Karius, he says, he continually falls back on his academic training to consider, "Am I asking the right questions? Do I have the right partners at the table? Is the question we aim to answer foundational?" He adds, "The value of having the right tools is amplified by having the right mindset and framing, both of which my academic journey provided in abundance."

Bercovici says there is a critical "science-to-technology assembly line" at the heart of the academia–industry relationship. Industry makes huge bets on diagnostic tests or drugs, leveraging specialized skills and technology that universities lack. "We see leapfrog moments across AI and genomics happening in private and public companies willing to spend hundreds of millions of dollars to make the necessary progress, which is relatively harder to match within academia," he says. At the same time, many fundamental discoveries are made in universities, where there are incentives for answering big questions rather than quickly maximizing financial returns. "In reality," Bercovici says, "we see both parties, academia and industry, benefiting from each other. The more we see that collaboration, the more value we will continue to unlock."



A former Azrieli Graduate Studies Fellow, Sivan Bercovici early in his career helped pinpoint genetic mutations that explained why African Americans have a four-fold risk of end-stage kidney disease.

Infectious disease diagnostics is an area primed for transformation. Typically, when doctors order tests for an infection, they search for one cause, say strep throat or COVID. But that requires doctors to have a good idea of what pathogen is responsible for a patient's illness. The approach does not work well when patients fall sick from a less common pathogen, which might not be on the doctor's radar.

Making matters worse, some tests for infectious diseases are unpleasant and even risky. One, known as bronchoalveolar lavage, requires a doctor to send a scope all the way down into the lungs, insert a small amount of saline, and then suction it back through the scope. Tests can also take several days to be processed, because fungi or bacteria need to grow in a lab before they can be identified. Patients can die waiting for the right answer.

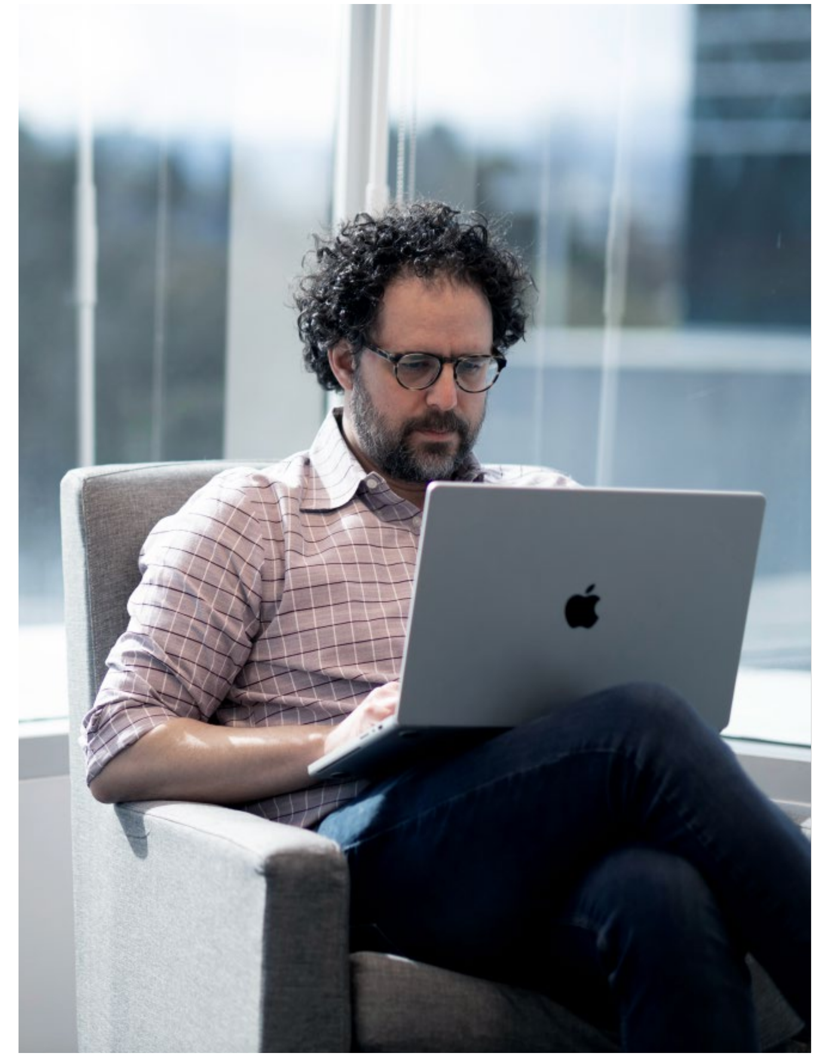
The Karius Test works differently. It is a type of liquid biopsy, a simple and non-invasive alternative to biopsies. It involves only a blood sample; the Karius Test looks not for a pathogen, which could be deep in the lungs, but for bits of DNA circulating in the bloodstream rather than in cells. And it uses machine learning to analyze and interpret that DNA.

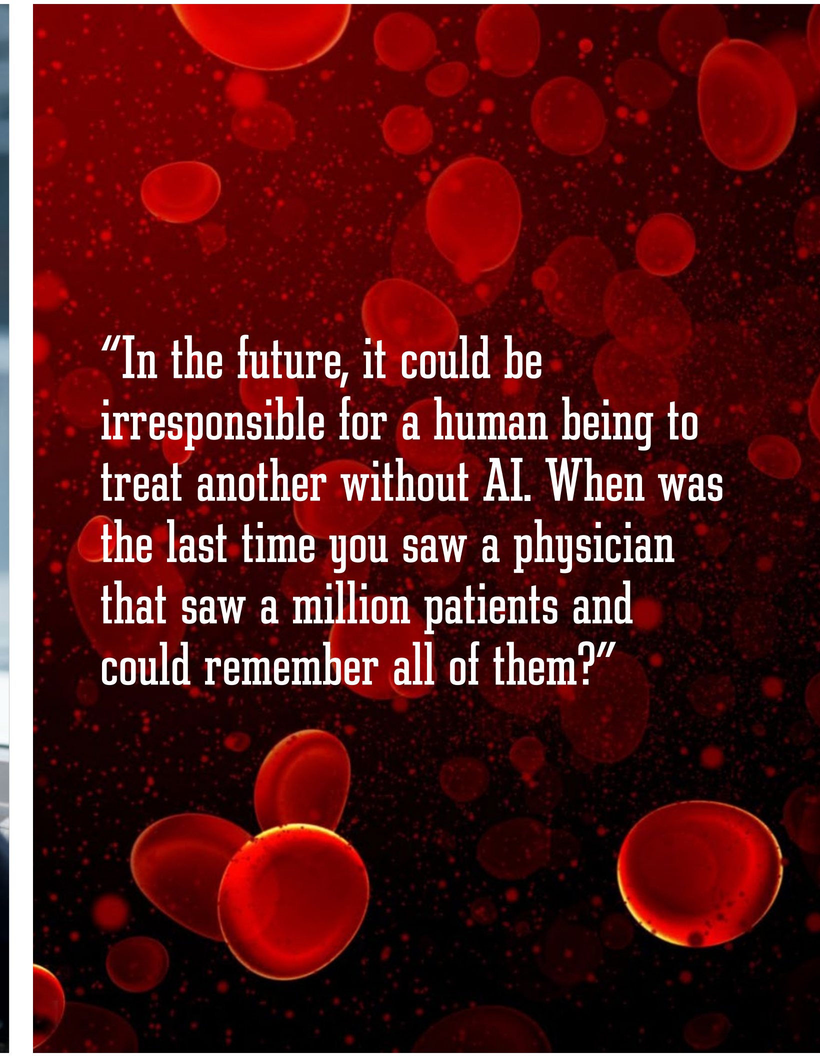
The ability to isolate and analyze cell-free DNA — released by cells as they die — is a recent development. Only in the last decade, for example, has cell-free fetal DNA screening become widely available. By picking up the DNA shed by the fetus that is circulating in the mother's bloodstream, the test checks for markers of genetic conditions. Cell-free DNA testing has also been developed for cancer and transplant health.

Karius is the first, and still only, firm to apply cell-free DNA testing to infectious disease testing. They have had to push the boundaries of current technology even further. Pathogens are microscopic, so they shed far less DNA than, say, a fetus. That was the first hurdle that Karius had to overcome through a combination of molecular biology breakthroughs and advanced statistical modelling. "Only 1 in 100,000 to 1,000,000 DNA particles in the blood are coming from microbes," says Bercovici. "The rest are coming from humans and contamination."

There are also germs circulating in the environment – sitting on the skin or floating in the air in a lab. Bercovici and his team had to develop machine-learning algorithms that could find metaphorical needles in haystacks as well as confirm that the microbe's DNA was coming from the patient's blood rather than the environment or testing materials.

To do this, the Karius team continuously studies control samples that are exposed to the same environment and laboratory processes as the samples from patients. The objective is "to catch whatever there is in the environment," as he puts it, "and create a statistical model of what that specific environment looks like." If the amount of bacterial or fungal DNA from a blood sample closely matches the amount found in control samples, it is unlikely to be the cause of the patient's infection. The test also compares DNA from microbes in blood samples taken from healthy people, to see what levels of "background" microbes are normal — those we carry that don't actually make us sick.





The second challenge involved in developing the test was determining when microbial cell-free DNA signals amounted to an actual infection. After all, we all carry trillions of microorganisms, including different gut bacteria or fungi that are either harmless or that our immune system will destroy before they hurt us. "We didn't want to send a report back to the physician that says, 'It's a hundred things,'" says Bercovici. "That's as useful as an empty report." So Bercovici and his team had to craft algorithms optimized to filter out cell-free DNA from microbes that are within the threshold of healthy controls, or could otherwise be explained by non-infectious sources.

The years of meticulous modelling, scouring academic databases for genetic information about unheard of pathogens and perfecting the AI algorithm have paid off. Many acutely ill and hospitalized patients, failed by conventional care, received Karius results that helped their physicians in the management of their care — from common yet otherwise undiagnosed cases of pneumonia to more rare cases, such as patients with atypical monkeypox whom doctors did not think to test because they did not present with the telltale lesions.

As Bercovici explains, the test is "agnostic." By screening for more than 1,000 microbes whose genetic material has been studied and included in an academic journal or scientific databases, the machine can pick up on pathogens a doctor would not necessarily think about.

The Karius Test is not a panacea. Sometimes it detects microbes that, while being in the sample, are not the cause of disease. Other times, it does not identify any potential pathogens, leaving doctors just as stumped. But, when combined with standard tests, Karius reduces the time to diagnosis and helps resolve more cases, producing results just one day after the blood sample arrives at headquarters.

While Bercovici is confident the venture will become sustainable with increasing adoption, he also wants to prioritize research that can have an impact on people's lives beyond the primary use cases, even if such projects do not have a big payout in the short term. For example, Karius has designed a specific test to screen pigs for pathogens ahead of pig-to-human organ transplantation — an experimental procedure that happens a handful of times a year. The test takes a bite out of Karius's bottom line but could ultimately support the emergence of xenotransplantation, which aims to address the substantial shortage in organs by using safe organs from animals.

Bercovici acknowledges the broader risk for medical science in relying so heavily on AI — AI-based systems trained on limited datasets could be inaccurate or biased, for example, diagnosing conditions in patients of some ethnic groups but missing or misdiagnosing them in others. But overall, he is optimistic about AI's impact on health.

"In the future, it could be irresponsible for a human being to treat another human being without AI," he says. "When was the last time you saw a physician that saw a million patients and could remember all of them? When was the last time you saw a physician that read all the papers that just came out today?" ▲●■

The Karius Test (above left), a type of liquid biopsy, involves a straightforward blood sample rather than an unpleasant and even risky test that some medical cases require. Bercovici has also helped design a test to screen pigs for pathogens ahead of pig-to-human organ transplantation.