Karius Aims to Diagnose Infection From Cell-Free Microbial DNA

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SAN FRANCISCO (GenomeWeb) – Startup Karius, which spun out from Stanford University in 2014, is collaborating with researchers to demonstrate that it can diagnose infection by identifying cell-free pathogen DNA in blood.

The Menlo Park, California-based company presented data from several of its academic collaborations at last week's American Society for Microbiology meeting in New Orleans. In addition, CEO Mickey Kertesz said in an interview that the firm is working with seven early-access partners who are evaluating the so-called Digital Culture test and that it is planning for a broader commercial later this year through its CLIA-certified and CAP-accredited laboratory.

Karius spun out of Stephen Quake's Stanford laboratory, launched by researchers who were studying whether cell-free DNA could be evaluated as a marker of rejection in transplant patients. In the course of that work, the researchers identified microbial cell-free DNA circulating in patients' blood. "We wondered whether this could be used for applications in infectious disease," Kertesz said. Kertesz was previously a cofounder and CEO of the long-read sequencing startup Moleculo, which was acquired by Illumina in late 2012.

Karius was launched in order to develop technology to use the circulating cell-free microbial DNA to diagnose infection. "Pathogens that infect humans shed DNA and RNA into the bloodstream," Kertesz said, "providing a great window into the infectome of a patient."

The goal of the company is to transform infectious disease diagnostics, which often relies on physicians making educated guesses and a series of trial and error diagnostic tests. "We want to replace this investigation process with one single test," Kertesz said.

Using sequencing to diagnose infectious disease is not a new concept and several companies and academic groups are pursuing their own strategies to commercialize NGS-based infectious disease tests, including Charles Chiu's team from the University of California, San Francisco and Aperiomics. However, Kertesz said that the use of cell-free DNA from blood is what sets Karius apart.

Last year, the firm, in collaboration with researchers at Duke University, published a case report in the journal Open Forum Infectious Diseases, describing using its technology to diagnose sepsis in a 60-year-old man within 24 hours.

The company currently offers two products to early access users: its Digital Culture test, which screens for more than 1,250 pathogens, including bacteria, viruses, fungi, and other eukaryotic pathogens; and a test for Mycobacterium chimaera, which was recently implicated in infections from open heart surgery.

The firm has intellectual property related to the molecular biology and bioinformatics portions of its test, both IP it licensed from Stanford as well as developed internally, Kertesz said. One major challenge in developing a test that evaluates cell-free microbial DNA was

figuring out how to separate the microbial DNA from a background that consists primarily of human cell-free DNA, Kertesz said. He declined to disclose details of the method the firm developed to do that, since it is proprietary, but said that there are physical differences between human and microbial genetic material that can be exploited in order to enrich the microbial DNA. After the enrichment, the microbial DNA is sequenced. Then, the company's bioinformatics tools match the sequences to microbial sequences in a reference database that consists of both publicly available genomes as well as the company's internally curated data. "The algorithm looks at the reads from each sample and then describes the distribution of microbes found in that sample," Kertesz said.

There are several advantages to this type of test over standard diagnostic tests, he said. For one, it does not rely on culturing the pathogen. Typically, when patients present with an infection, clinicians try to culture the pathogen in order to diagnose the disease, but more often than not, the bacteria are unculturable. In addition, he said, Karius' test doesn't require a priori knowledge about the infecting culprit, and finally, it avoids invasive biopsies. For patients whose infections are in their lungs, heart, or brain, often the tissue needs to be biopsied, an invasive and costly procedure.

Karius is collaborating on a clinical trial with researchers at the University of California, San Francisco, to evaluate the ability of its test to identify infection in patients who have received a stem cell transplant.

Peter Chin-Hong, an infectious disease physician at UCSF, said that his group is running the Digital Culture test in the 100-patient pilot study alongside traditional tests typically used to monitor immunocompromised patients after stem cell transplantation, including blood cultures and a cytomegalovirus test.

Although the team only has results from the first 10 patients, he said that so far, the test appears promising. "It obviates the need of having to choose specific tests to run," he said. Although blood cultures can look for multiple pathogens at once, they don't detect all potential infections, he explained, so physicians have to choose what tests to run. From the first results, he said, it seems that the Digital Culture test is "detecting things before clinicians begin to think about testing for them."

Chin-Hong described one patient in particular for whom the Karius test uncovered an unexpected infection. The patient, who had received a stem cell transplant, returned to the hospital because he was having urologic problems. The cause was thought to be due to some kind of obstruction, either inflammation or a mass, Chin-Hong said. He underwent a number of different interventions to look for the obstruction, to no avail. The Karius test, meantime, pointed to a different cause — a chlamydia infection. "This was surprising because normally, chlamydia doesn't act so dramatically," Chin-Hong said. Most likely, the patient had the infection prior to undergoing the stem cell transplant, but did not know about it, he said. The infection likely did not cause symptoms until the patient was immunocompromised.

In another case, a patient who was experiencing fever and other symptoms pointing to an infection was evaluated via Karius' test, as well as standard blood culture techniques. The Karius test identified Staphylococcus aureus, which was confirmed via the blood culture. But, importantly, the Karius test made the diagnosis earlier than the blood culture. "This was faster than traditional technology, so that's a good proof of concept," Chin-Hong said. "Outcomes are typically better the earlier an infection is detected and can be treated."

Chin-Hong said it is still too early in the pilot study to draw hard conclusions about the test, but the early results are promising. The full results of the study are expected in the next six months.

If the remainder of the study is successful, he said, he could envision using the Karius test as a "one-stop shop" to replace the suite of tests currently performed to diagnose infection. "It could help consolidate many of the tests we currently run," he said. However, not all tests would be replaceable: imaging and radiology tests, for example, would still play an important role, he said.

Aside from the collaboration with UCSF, the firm is collaborating with Stanford University on a clinical trial to determine the etiology of sepsis.

In addition, Kertesz said that the firm has been working with the US Centers for Disease Control in response to an outbreak of Mycobacterium chimaera. The outbreak was caused by contaminated equipment that is used in open heart surgery. Last year, the CDC issued a warning letter to healthcare providers that a device used in open heart surgeries known as a heater-cooler unit may have been contaminated during the manufacturing process. Around 60 percent of such surgeries use devices at risk for contamination, and the risk for infection is between 1 in 100 and 1 in 1,000, the CDC warned.

In response, Karius developed a noninvasive blood test that uses the same cell-free DNA technology as the Digital Culture test but is specific to M. chimaera. That test is currently used to test patients with symptoms of infection, but Karius is also in discussions with the CDC about other potential uses of the test — for instance, to screen patients before they have symptoms.

Thus far, Kertesz said, the Karius test has identified M. chimaera infections in five out of six patients with symptoms, compared to just one out of six tested via standard blood culture.