Diagnosis on Day Zero

The winner of AACC's 2021 Disruptive Technology award married machine learning and genomics to rapidly identify bloodstream infections.

BY KAREN BLUM

What if laboratories and clinicians had access to a testing platform that could rapidly diagnose bloodstream infections such as sepsis directly from blood samples within hours of a patient being admitted to the hospital? That was the idea behind Day Zero Diagnostics' DZD OneSeq Dx platform. The Boston-based company received AACC's 2021 Disruptive Technology Award for its efforts.

The honor, which recognizes innovative testing solutions that improve patient care, was presented during the AACC Annual Scientific Meeting & Clinical Lab Expo in Atlanta.

"It was incredibly exciting," said Jong Lee, MBA, the company's CEO and cofounder, of the win. "It was a great competition, and it was in the company of other competitors who we consider to be very high caliber, all doing something on the cutting edge of science."

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OneSeq Dx uses whole genome sequencing and machine learning to rapidly diagnose infections directly from blood samples, without the need to wait for culture results. The goal is to help patients with severe infections receive the most effective antibiotic on the first day they are admitted to the hospital—"day zero."

The product's idea stemmed from an identified clinical need, Lee said. His former college roommate, Doug Kwon, MD, PhD, (scientific cofounder of Day Zero) is an infectious disease physician at Massachusetts General Hospital who regularly sees patients with bloodstream infections. Kwon was frustrated by what he found to be a lack of good diagnostic information to work with. At the time, Melis Anahtar, MD, PhD, (another scientific cofounder) was conducting next-generation sequencing work in Kwon's lab on the microbiome of women at high risk of HIV acquisition.

The two of them got to talking about how illogical it is that you can get high-resolution diagnostic information via sequencing in the lab, but you're completely unable to get that type of information for clinical use as an infectious disease physician, Lee said. "That was the genesis of them starting to think about how to apply next-generation sequencing (NGS) to the problem of infectious diseases."

OneSeq Dx processes blood samples using ultra-high enrichment (at the level 10^9) to extract high yields of bacterial DNA directly from clinical samples that may contain up to a billion times more human DNA than bacterial DNA, Lee said. Then, the DNA is sequenced using NGS.

Once sequencing data is obtained, it's run through two machine learning algorithms to interpret the sequencing data and offer high accuracy species identification and antibiotic resistance profiling. Keynome ID determines the species of infections at concentrations as low as 1CFU/mL, while Keynome g-AST (genomic antibiotic susceptibility testing) determines the antibiotic resistance and susceptibility profile. Results can be obtained in as little as 6–8 hours.

"At the end of the day, what we're trying to do is provide an answer that is very similar to the gold standard answer that you would have been able to get from culture, but in a much shorter timeframe," Lee said, "and potentially even in situations where culture may not grow."

The company is trying to tackle two related problems in infectious disease diagnostics, said Lee. One is antibiotic resistance, what he calls "the other pandemic." For testing done using culture, it takes 2–5 days to get to an antibiotic resistance profile for an infection. Antibiotic resistance is particularly challenging in bloodstream infections such as sepsis, Lee said, with patients decompensating by the hour. Clinicians generally are "flying blind," Lee said, using a "carpet bombing" approach to try to subdue severe infections. The only guide to drive treatment decisions at times are just the aggregate infection patterns typically seen at the local hospital and community.

Through OneSeq Dx, "we're trying to provide physicians a solution that gives them a definitive species

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ID and antibiotic resistance profile in hours rather than days, so that they can treat patients on the first day that they're admitted to the hospital," he said. "The holy grail in this space is to diagnose directly from blood rather than from blood culture."

Due to the high amount of background human DNA, extracting infection information from blood can be challenging, like finding the proverbial needle in a haystack, Lee explained. Some companies attempting to diagnose infections from blood have tried approaches like using probes designed to attach to specific biomarkers to work like a magnet, extracting the needle. While that can work, Lee said, it will identify only the biomarkers being targeted, and only provide very limited information— not the whole genome of a bacterial pathogen. It could help with species identification, but it won't be comprehensive. And it cannot provide comprehensive antibiotic resistance profiles.

Day Zero takes the opposite approach, Lee said: "Our technology is designed to remove all the straws of hay, so that you're agnostically left with whatever the needles are—the bacterial pathogens that drive the infection. That's the trick of ultra-high enrichment."

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Combining this process with the company's machine learning algorithms provides a novel approach to learn from data on all of the various factors that could result in resistance and susceptibility. For example, whole genome sequence data for each patient's pathogen can be aggregated to help clinicians amass an epidemiological view about what infections are running through their hospitals or local regions, Lee added. "It becomes a surveillance service that can help a lab make early determinations of outbreaks."

The company is now working on product engineering, incorporating their testing capabilities into a device that can be used in microbiology labs. Once a design is set, they'll pursue Food and Drug Administration approval.

People have talked about using sequencing for clinical diagnostics for years, but it's still primarily used for research applications, Lee said. "We think these enabling technologies we're developing are the kind of technologies that allow sequencing to really develop deep integration into clinical microbiology. You can think of what we do as focusing on developing the enabling technology that makes sequencing usable for everyday clinical decision-making."

The two other finalists for the award were recognized for developing new technologies for the SARS-CoV-2 virus: MeMed for its COVID-19 Severity test and Mammoth Biosciences for its CRISPR-based DETECTR BOOST platform.

MeMed, based in Haifa, Israel,uses host-response profiling and machine learning algorithms to create a novel test to stratify the risk that a patient with COVID-19 will experience severe outcomes. It measures three circulating proteins that indicate infection and inflammation. Serum samples are applied to a cartridge and inserted into a MeMed platform called MeMed Key that analyzes amounts of these proteins and applies machine learning algorithms to provide a score up to100. The higher the score, the higher the likelihood of a severe outcome. The test, approved in Europe, delivers results within 15 minutes and can help clinicians predict outcomes up to 2 weeks out, helping them decide whether to escalate treatment, admit patients to the hospital, or send them home.

Mammoth Biosciences is pursuing a high-throughput, CRISPR (clustered regularly interspaced short palindromic repeats)-based test to identify the presence of SARS-CoV-2. The company's DETECTR BOOST platform uses CRISPR, a gene editing technology that has been repurposed for diagnostics, to search patient samples for the presence of specific nucleic acids that are indicative of disease. First, the company pairs a CRISPR-Cas protein with a guide RNA that matches the exact sequence they want to detect. If the Cas/guide RNA complex finds its target sequences, Cas proceeds to cut the matching DNA or RNA. Some Cas proteins also chop up nearby pieces of genetic material, including reporter molecules that let scientists know they found their target sequence. The company is developing a turnkey workstation to run the assay, with the ability to perform thousands of tests per day.

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