A Blood Scan for Sepsis?

Molly Webster[1] and Vikram Sheel Kumar[2*]

Each day, we carry up to 6 pounds of microorganisms around inside our bodies. Most of the time, this microbiome is kept in check by our immune system. But age, surgery, or chronic disease can weaken our immune system, giving these microorganisms a chance to gain hold. Under the right (or wrong) conditions, this microbial coup (or bad foreign bugs) can cause sepsis.

Each year, sepsis strikes 1 million Americans, and can kill up to half of those patients. That's more than AIDS, prostate cancer, and breast cancer combined. Mortality is reduced when the cause of the infection—the specific species of bacteria or fungus—is quickly identified and targeted medications are given.

"For every hour sepsis goes undiagnosed, mortality increases by eight percent," says scientist Tom Lowery. "Differences in time of identification could impact the mortality of patients." Yet today's gold standard sepsis tests can take 2–5 days to identify the basis for infection.

Enter Lowery and the team at T2 Biosystems, a company that is using patented nanotechnology-based T2 magnetic resonance (T2MR) for the "detection of pathogens, biomarkers, and other abnormalities in a variety of unpurified patient sample types." Lowery is their chief scientific officer.

In September 2014, the US Food and Drug Administration approved the company's first technology: the T2Candida Panel, a test that promises to identify, within hours, fungal infections that can cause sepsis *(1)*. Here, we consider T2Candida and its potential in the laboratory.

What Is the Innovation?

The T2Candida Panel is a nonoptical, non–culture-based approach to diagnosing 5 relevant species of *Candida*. Obviously, when you eliminate cell culture, you eliminate the time it takes for your test to supply an answer. But why MR?

Essentially, says Lowery in an email to *Clinical Chemistry*: "MR can go inside someone's blood sample, and based on the physics of how measurement is taken, the electronics are not affected by anything that absorbs light, circumventing background noise," potentially allowing you to see an infection more clearly.

Maiken Cavling Arendrup

"It is agnostic to matrix effects," says Lowery.

Plus, "so much of how we use reagents and assays is defined by optical detectors," he says, "when you have nonoptical, you can take a reagent that is commonly used and use it in a different way."

For their specific system, the company is using T2 measurements, a standard MR technique that takes measurements of the relaxation of water molecules in the presence of magnets to identify infection. The T2Candida Panel is run on the T2Dx Instrument, a 3- by 2- by 2-foot box that uses T2MR in its analysis (Fig. 1). The box itself is pretty straightforward: there are 7 front compartments, or drawers, and it contains a permanent magnet, about as big as a Rubik's cube, says Lowery.

The company's website boasts that this product is rapid, simple, and sensitive. T2Candida can detect 1 cfu/mL, far outshining current tests, which in best-case scenarios detect 30 cfu/mL, but on average detect around 100 cfu/mL. Which is a significant difference, says Lowery, because a person is considered septic at 1 cfu/mL.

How Does It Work?

Eleftherios Mylonakis

To run the T2Candida Panel, the microbiologist takes 4 mL blood directly into an EDTA Vacutainer Tube, inserting the unit in 1 of the front drawers (Fig. 2). Inside the T2Dx instrument, patented reagents in the cartridge lyse the cells within the matrix. The resulting debris—or what the team affectionately calls *gemisch* (German for "junk," says

[1] Freelance writer, Brooklyn, NY; [2] Department of Laboratory Medicine, Boston Children's Hospital, Boston, MA.
* Address correspondence to this author at: 390 Commonwealth Ave., Apt. 605, Boston, MA 02215. E-mail vkumar@dimagi.com.
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Fig. 1. The T2Dx Instrument 2015.

Lowery)—is packed into a 50-μL pellet, "a reddish goo" containing everything from white cell nuclei to still-intact whole-cell pathogens.

Lowery describes this pellet as a paradigm shift. "It is a paradigm shift because all other platforms process the supernatant and discard the pellet," he says. "The rest of the experiment is done on the pellet, because that is the most efficient way to concentrate the target pathogen cells."

Applied reagents contain superparamagnetic particles, and when a *Candida* pathogen is present, the particles will clump around its amplified DNA product. This clumping will change the T2 relaxation measurements. Five hours later, results are displayed on a touchscreen

Fig. 2. The T2Dx Instrument with T2Candida Panel seated in Stat Drawer.

interface. The gemisch is neutralized with a bleach solution, popping out the back of the machine for disposal *(2)*. "It's like an Easy Bake Oven for sepsis diagnosis," says Lowery.

In the recently published clinical trial study of approximately 1800 patients using this device, the authors achieved an overall specificity per assay of 99.4% and sensitivity of 91.1%, while achieving a diagnosis in <5 hours. Across all studies to date, T2Candida has successfully detected invasive candidiasis in 53 of 55 cases, whereas blood culture detected only 33 of 55 *(1)*.

"Overall, the T2Candida panel is a welcomed addition to the diagnostic armamentarium, which has the potential to help diagnosing more patients with invasive candidiasis earlier," write Dr. Maiken Cavling Arendrup and Dr. Bart-Jan Kullberg in an email to *Clinical Chemistry*. Dr. Arendrup is head of the mycology unit at the Statens Serum Institut, and Dr. Bart-Jan Kullberg is head of the Radboud Institute for Molecular Life Sciences; together, they recently wrote a piece on invasive candidiasis for the *New England Journal of Medicine (3)*.

There are 2 major benefits to the T2Candida Panel, they write: first, "the rapid turnover time allowing a same day result for most samples, whereas blood culture often requires two days of incubation or even longer before *Candida* is detected"; and second, it has "a high analytic sensitivity for the species included."

Additionally, "in order for a microbiology department to be able to run the test frequently enough that they can provide information to clinicians, the test has to be easy to perform and interpret," says Dr. Eleftherios Mylonakis, chief of infectious diseases and professor of medical sciences at Rhode Island Hospital and the Miriam Hospital, Alpert Medical School of Brown University, and lead author on the study *(1)*. The T2Candida Panel is "test easy," he says.

Where Can This Technology Fit in The Laboratory?

As of September 2015, the T2Candida Panel is being used by 6 hospitals, and 19 others are under contract to bring the system into their laboratories.

"We're targeting hospitals with the largest high-risk population," says Lowery, which are some 450 hospitals spread across the US. Because it's a brand new technology, hospitals will take time to evaluate it not only as a mortality reducer, but also its cost efficiency. A recent analysis published in *Future Microbiology* indicates that the tests saves $1148 per tested patient, and that there's a 60% mortality savings *(2)*. "This assay does provide significant and clinically relevant information," says Dr. Mylonakis.

Tom Lowery

According to Drs. Arendrup and Kullberg, the drawbacks to the T2Candida Panel are that "susceptibility testing is not possible, and that not all human pathogenic species are included."

Looking forward, the T2 Biosystems team is creating a sepsis bacteria panel, as well as applying the T2MR technology to other diseases, such as Lyme.

"This technology can provide all the information blood culture provides," says Lowery. "Pick your infectious disease test and we can do it."

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References

1. Mylonakis, E, Clancy CJ, Ostrosky-Zeichner L, Garey KW, Alangaden GJ, Vazquez JA, et al. T2 magnetic resonance assay for the rapid diagnosis of candidemia in whole blood: a clinical trial. Clin Infect Dis 2015;60:892–9.
2. Pfaller MA, Wolk DM, Lowery TJ. T2MR and T2Candida: novel technology for the rapid diagnosis of candidemia and invasive candidiasis. Future Microbiol 2016;11:103–17.
3. Kullberg BJ, Arendrup MC. Invasive candidiasis. N Engl J Med 2015;373:1445–56.

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