Inflammatix Immune Response Tests Could Enable Antibiotic Decisions in One Hour

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NEW YORK (GenomeWeb) – Burlingame, California-based Inflammatix is taking a different approach from potential competitors in developing a sepsis diagnostic test that could enable physicians to decide within one hour whether the infection is bacterial or viral, and informs on the need to prescribe or withhold antibiotics.

The company's HostDx Sepsis test uses quantitative multiplex gene expression to analyze a patient's immune system, or the host response, rather than looking for the presence of a pathogen that indicates whether there is an infection in the blood, a method employed by many companies in the sepsis testing market.

The firm, founded in 2016 as a spinout from Stanford University, expects to have a CE-marked commercial sepsis test available for use by hospitals in emergency and intensive care settings in 18 to 24 months, its CEO and cofounder Timothy Sweeney said in an interview.

The firm's assays, running on a molecular, multiplex platform, read patterns of gene expression from white blood cells as an indicator of the immune system's response to infection. Its multigene sepsis diagnostic panel would be able to tell from a blood sample whether a hospitalized patient has a bacterial, viral, or no infection so that physicians would be able to administer more appropriate treatments earlier. It would also allow physicians to evaluate the serious nature of the infection and a patient's risk of mortality, so that they can better stratify their patients.

Just as important, Sweeney noted, the company has established a method for test development that involves analyzing raw data in public and private databases and identifying the most accurate sets of genes for diagnosing a given infectious disease. It has plans to use the approach to develop several other tests, including assays for tuberculosis, malaria, and dengue.

"Inflammatix has developed a method that is broadly applicable and gives us the ability to not only discover the best gene sets for specific applications, but also the best algorithms that sit on top of those gene sets to make sure that the diagnostic tools are accurate," Sweeney said.

The firm has prospectively validated eight sets of genes for different clinical applications, he said.

Inflammatix is also developing a test that would enable physicians to decide whether to administer antibiotics for a patient presenting with fever in doctors' offices. Depending on the commercial strategy that the company undertakes, the fever test could be on the market prior to the sepsis assay, the firm's Cofounder and Chief Operating Officer Jonathan Romanowsky said in an interview.

Because the fever test would be applied as a screening or triage tool by a physician who suspects a patient has an infection, its turnaround time is less than 30 minutes, Sweeney said.

That necessitates working with partners who are building platforms that can rapidly measure gene expression.

"By reading the immune response, you can tell whether a bacterial or viral infection is causing a patient's symptoms, and fundamentally that's what a physician needs to know up front," Sweeney said. He noted that the firm has signed collaboration agreements with undisclosed partners that are already building platforms suitable for integration of Inflammatix's assays.

The firm said that its HostDx fever test has been validated in 38 retrospective cohorts, and six prospective cohorts are currently enrolled for its validation. The firm published its validation results in *Science Translational Medicine* with an additional paper forthcoming in *Nature Communications*.

The firm said it has validated the HostDx Sepsis test in 20 cohorts of 1,057 patients. It has also demonstrated its performance in five cohorts of 189 patients diagnosed with sepsis at the time of hospital admission and four cohorts of 282 patients with hospital-acquired sepsis.

For its fever assay, the firm has reported 94 percent sensitivity and 76 percent specificity for bacterial infection. For its sepsis assay, it has reported 94 percent sensitivity for bacterial infection, 91 percent specificity for viral infection, and 95 percent sensitivity for 30-day mortality related to sepsis.

A different approach

Sepsis leads to high rates of mortality, progresses quickly within the body, and is dependent for effective outcomes on rapid diagnosis and treatment usually with antibiotics.

Sweeney and Romanowsky said that they believe Inflammatix's approach and technology affords an advantage over other tests currently available and in development.

Many diagnostic tests in development or production for analyzing patients with sepsis rely on looking for known pathogens, Sweeney said. The closest competing tests to HostDx's approach from a technical perspective uses procalcitonin as a biomarker. Like HostDx's approach, such tests rely on reading the host response for a diagnosis.

Several FDA-cleared procalcitonin tests are on the US market today and are used by physicians for diagnosing sepsis, including those produced by Roche, BioMérieux, and Thermo Fisher Scientific.

But while procalcitonin looks at the immune response for detecting bacterial sepsis, "it's not clear which part of the immune response it's looking at," said Sweeney, who is a licensed physician and data scientists with more than 10 years of experience researching sepsis. "Like most biomarkers for sepsis, it conflates the likelihood of the presence of an infection with its severity," and a patient with pneumonia can have high levels of procalcitonin. People with severe burns can have even higher levels, even when the procalcitonin levels are not linked to sepsis in either case.

According to Sweeney, the discovery of procalcitonin as a biomarker for sepsis diagnosis did not undergo the robust bioinformatics-driven methods that Inflammatix used to develop its gene expression assay to establish a biomarker signature for sepsis.

The firm leverages data science, machine learning, and artificial intelligence to develop and validate the clinical algorithms that power the company's diagnostic tests.

The development of the tests relies on a targeted approach that enables the firm "to be as specific as the data will possibly allow," Sweeney said. "In our studies, we've demonstrated a rule-out capability that's three-times better than procalcitonin."

In developing its tests, Inflammatix analyzes microarray and RNA-sequencing data that reside in public and private databases and that are derived from several patient cohorts around the world. Its data science team observes patterns or fingerprints of gene expression across different cohorts. "When you can find a single fingerprint that remains true in different countries and at different ages and with different severities of infection, you've identified a signature that [can be generalized] and will work when you validate it in a new patient population," Sweeney said.

In the first peer-reviewed papers, Inflammatix executives, including Sweeney and co-founder Purvesh Khatri, described searching for the best gene that separates these types of patients across all cohorts, and then searching for the next best gene that similarly separates these types of patients. "We let the algorithm run in that fashion until we can't improve the signature anymore," Sweeney said.

Inflammatix's work on HostDx has culminated in an assay that could determine whether a patient has a bacterial or viral infection and how sick the patient is, Sweeny said. Those genes were published in a series of papers, and the selection is locked in place, he added.

The firm's HostDx sepsis test's ability to separate the likelihood of having a bacterial infection from the severity of the infection would be in high demand as antimicrobial resistance becomes a greater global concern, Sweeney said.

"If you … have a situation where a patient comes into the hospital who's suspected of having sepsis," Sweeney said, "[u]sing the HostDx test, a physician might find that the patient has a bacterial infection, but it's not severe and the patient could be released, which eliminates an unnecessary hospital stay and the use of antibiotics. That's something that doesn't exist in the market."

While diagnosing infections, clinicians frequently use blood culture testing to find pathogens, which can take up to 72 hours to get a positive test result, compared to one hour with HostDx, Sweeney said. Additionally, only about 30 percent of inpatients who are judged to have bacterial infections actually have bacteria in the bloodstream, he added. "The gold standard is blood culture, but it’s falsely negative in most patients who have bacterial infections," he said.

Although a lot of companies are focused on developing and producing more rapid tests for bacteremia, a patient might still need an antibiotic when those tests produce negative results, Sweeney noted.

And there are also limits to sepsis tests that rely on pathogen detection after a blood culture. "If the panel doesn't have the bug you're seeking, its test is blind to it. If you are using something like deep sequencing to look for DNA in the bloodstream, you can frequently amplify things that cannot be interpreted."

Current focus

Inflammatix is currently focusing resources on writing new algorithms to make its sepsis and fever tests even more accurate, and building assays to measure its gene expression targets rapidly "to get them the clinic and help doctors treat patients," Sweeney said.

"As a small company we can't do too many things at once," he said. "As the sepsis and fever tests approach the market, then we can begin to focus on the rest of the pipeline. Our hope is that as the signature discovery team completes its work on one assay, they can move onto the next area of discovery, and as the assay team completes development of one assay they can also move on to the next."

Inflammatix has an exclusive license to the sepsis biomarkers from Stanford, and it has completed a Series A financing for an undisclosed amount led by Khosla Ventures with participation from the Stanford-StartX fund. Inflammatix also secured a Small Business Innovation Research grant for an undisclosed amount from the Defense Advanced Research Projects Agency of the US Department of Defense.

Sweeney noted that the company has adequate funding to take it through most of this year, but that it is initiating another financing round for an undisclosed value that would take it through CE marking of its sepsis test.

According to the firm, its fever and sepsis tests will target a collective market of an estimated 100 million patient visits each year in the US alone.