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Eurofins Viracor Test Measures T-Cell Response to Determine COVID-19 Immunity

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NEW YORK – While vaccines for SARS-CoV-2 have rolled out at home and abroad, there is still uncertainty about their long-term effectiveness against the virus, and questions linger about whether a booster shot will be necessary and how often individuals will need to get vaccinated to remain protected against the virus.

Against this backdrop Eurofins Viracor has developed a test that looks at the reactivity of live T cells to help measure patients' immunity after getting vaccinated, joining the ranks of other companies, such as Oxford Immunotec and Adaptive Biotechnologies, that have also developed T-cell tests to help answer questions about individuals' immune response to the coronavirus.

Eurofins Viracor's test, called the InSight T Cell Immunity Test, is a flow cytometry and intracellular cytokine staining test that looks at the reactivity of live C4+ and CD8+ T cells collected directly from whole blood to the SARS-CoV-2 spike and nucleocapsid proteins to measure a patient's cytokine response and determine levels of immunity.

The test measures three cytokines — interferon-gamma, interleukin-2, and TNF alpha — which indicate an immune response to SARS-CoV-2, said Eurofins Clinical Diagnostics CSO Steve Kleiboeker. Cytokines are the markers of immune response in vaccinated and recovered people, and if T cells produce one or a combination of the cytokines, that's "a demonstration of specific immunity," he said.

Eurofins' test provides "an objective assessment of whether a patient has an immune response to SARS-CoV-2," he added, with results that give clinicians a summary statement of whether immunity was detected, as well as details about spike and nucleocapsid reactivity, and cytokine levels and responses in a patient's blood.

Using four different sample aliquots, the cells are individually stimulated by spike and nucleocapsid peptide pools to measure intracellular cytokine responses and compared to negative controls of blood samples, Kleiboeker said. The cells are stained with a fluorescent dye that recognizes the three cytokines, he said. The value of the stimulated sample divided by the negative control is called the stimulation index, which is included in the lab report for the clinician and provides more detailed information about the immune response.

The laboratory-developed test is targeted toward immunocompromised people and transplant patients who have had to be immunosuppressed. Kleiboeker said these groups often don't respond to vaccines nearly as well as an immunocompetent person, so the test can be used to see if they've responded to and are protected from the virus. If they're not protected, a clinician could re-vaccinate or try a different vaccine, he said.

He added that the test is intended for inpatient use at hospitals, although it could also be used in follow-up visits post-transplant.

Part of the benefit to hospitals is the ability to provide a highly specialized test without having to create and run it on their own, Kleiboeker said. There's "little value" in establishing a test like this locally since it's so complicated to perform, and Eurofins has a relatively quick turnaround for the test — once the test is received, results are reported the next day, he said.

Eurofins isn't new to T-cell test development, as it has been providing a similar test for cytomegalovirus for five years, Kleiboeker said. That test is also run for the transplant populations, and the SARS-CoV-2 test was modeled after the CMV test.

The necessities for developing the COVID-19 test involved getting SARS-CoV-2 peptide pools and experimenting with the optimal levels to stimulate the cells, as well as optimizing the flow cytometry assay to measure the responses, he

said. The test currently has a sensitivity of 90 percent and a specificity of 78 percent, although Eurofins is in the middle of setting up studies for clinical assessment to further refine the test's accuracy, he said.

While there are numerous antibody-based tests on the market that provide a picture of an individual's antibody response to SARS-CoV-2 infection, the number of T-cell tests for such a purpose is much more limited. T cells, Kleiboeker said, are "more strongly associated with protection" and have a "higher correlation with freedom from infection and disease" than antibodies. They also tend to last longer in the body, he added.

Antonio Bertoletti, a professor at Duke-National University of Singapore Medical School who has studied T-cell response to COVID-19, said via email that antibodies and T cells are "two different components of the immune system," and the level of antibodies and T cells don't always correlate, as some individuals have "high antibody titers and low T cells" while others have high T cells and low antibodies.

He noted that T cells "are indispensable because [they] are not only essential to promote antibody production and maturation of B cells producing antibodies … but also for killing directly virus-infected cells."

He added that it "is likely that T cells are therefore extremely important to control the severity of the disease." The cells "don't prevent infection but they suppress viral replication and this makes disease less severe," he said.

When it comes to what is better for protection, Bertoletti, who was not involved in developing Eurofins' test, said no one really knows. "It is clearly better to have both, and this also means that having a low level of antibodies does not mean that you are not protected," he said.

T cell tests can be performed via a number of modalities, including flow cytometry, ELISPOT, and ELISA, but Eurofins chose flow cytometry because it can differentiate between different CD4 and CD8 T cells, Kleiboeker said. The Oxford Immunotec test uses ELISPOT technology, while the Adaptive test uses next-generation sequencing.

Kleiboeker noted that the Eurofins and Oxford Immunotec tests haven't been compared side by side or in a head-to-head study, so he couldn't make a claim about one's effectiveness versus another.

An issue with ELISA tests, meanwhile, is that they often produce false positives and indeterminate results, he added.

If immune responses were very rare, test developers would likely use ELISPOT for the test, but because several cells out of the 20,000 cells measured are going to fluoresce or react in Eurofins' test, it decided to use the technology, Kleiboeker said.

Bertoletti noted that "there is no best method" because "the different methods give different information and require different time" to results. For tests that "want to go deep in a few samples," flow cytometry and intracellular cytokine staining are a good option. But for an easier test that can be applied to large numbers of samples, rapid cytokine assays are the way to go.

Bertoletti said that T-cell analysis "is much more complicated than antibodies" because it requires the separation of peripheral blood mononuclear cells from blood, along with complicated methods of analysis. He added that "this method based on intracellular cytokine staining … can be performed only by very specialized laboratories," and that he is "not convinced that it will make things easier."

One of the "key unknowns" right now about the vaccines is how long immunity lasts, he said, and T-cell tests can provide an objective measure to determine the answer. Kleiboeker's current guess is that a yearly booster shot will be necessary, but additional data will be needed before any health agencies can make that decision.

Measuring both T cells and antibodies in vaccinated people "will become very important … to understand the level of immunity induced by the different preparation and whether we need a further boost after different times," Bertoletti said. "However, remember that at the moment we don't have any idea of the correlate of protection," or the level of antibodies and T cells necessary for protection, he added.

Researchers are also studying whether T cells "can be inhibited by mutations present in viral variants," Bertoletti said. He noted that T cells usually recognize different parts of viruses, and single mutations often don't completely abolish the recognition of the different T cells induced by the vaccine.

But he added that "some individuals can have responses more focused on the sections of the virus that are mutating," and that there is a need for more research on whether T cells induced by vaccines can be altered by variant

mutations.

"We need to keep analyzing and studying these parameters," he said.

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