Biological 'fingerprints' of long COVID in blood could lead to diagnostic test

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Markers in our blood—'fingerprints' of infection—could help identify individuals who have been infected by SARS-CoV-2, the coronavirus that causes COVID-19, several months after infection even if the

individual had only mild symptoms or showed no symptoms at all, say Cambridge researchers.

The team has received funding from the National Institute for Health Research to develop a test that could complement existing antibody tests. They also aim to use similar biological signatures to develop a test and monitor for long COVID.

While most people recover from COVID-19 in a matter of days or weeks, around one in ten people go on to develop symptoms that can last for several months. This can be the case irrespective of the severity of their COVID-19—even individuals who were asymptomatic can experience so-called 'long COVID."

Diagnosing long COVID can be a challenge, however. A patient with asymptomatic or mild disease may not have taken a PCR test at the time of infection—the gold standard for diagnosing COVID-19—and so has never had a confirmed diagnosis. Even antibody tests—which look for immune cells produced in response to infection—are estimated to miss around 30% of cases, particularly among those who have had only mild disease and or beyond six months post-initial illness.

A team at the University of Cambridge and Cambridge University Hospital NHS Foundation Trust has received £370,000 from the National Institute for Health Research to develop a COVID-19 diagnostic test that would complement existing antibody tests and a test that could objectively diagnose and monitor long COVID.

The research builds on a pilot project supported by the Addenbrooke's Charitable Trust. The team has been recruiting patients from the Long COVID Clinic established in May 2020 at Addenbrooke's Hospital, part of Cambridge University Hospital NHS Foundation Trust.

During the pilot, the team recruited 85 patients to the Cambridge NIHR COVID BioResource, which collects blood samples from patients when they are first diagnosed and then at follow-up intervals over several months. They now hope to expand their cohort to 500 patients, recruited from Cambridgeshire and Peterborough.

In their initial findings, the team identified a biomarker—a biological fingerprint—in the blood of patients who had previously had COVID-19. This biomarker is a molecule known as a cytokine produced by T cells in response to infection. As with antibodies, this biomarker persists in the blood for a long time after infection. The team plans to publish their results shortly.

Dr. Mark Wills from the Department of Medicine at the University of Cambridge, who co-leads the team, said: "We need a reliable and objective way of saying whether someone has had COVID-19. Antibodies are one sign we look for, but not everyone makes a very strong response and this can wane over time and become undetectable.

"We've identified a cytokine that is also produced in response to infection by T cells and is likely to be detectable for several months—and potentially years—following infection. We believe this will help us develop a much more reliable diagnostic for those individuals who did not get a diagnosis at the time of infection."

By following patients for up to 18 months post-infection, the team hopes to address several questions, including whether immunity wanes over time. This will be an important part of helping understand whether people who have been vaccinated will need to receive boosters to keep them protected.

As part of their pilot study, the team also identified a particular biomarker found in patients with long COVID. Their work suggests

these patients produce a second type of cytokine, which persists in patients with long COVID compared to those that recover quickly and might be one of the drivers behind the many symptoms that patients experience. This might therefore prove to be useful for diagnosing long COVID.

Dr. Nyarie Sithole, also from the Department of Medicine at the University of Cambridge, who co-leads the team and helps to manage long COVID patients, said: "Because we currently have no reliable way of diagnosing long COVID, the uncertainty can cause added stress to people who are experiencing potential symptoms. If we can say to them 'yes, you have a biomarker and so you have long COVID," we believe this will help allay some of their fears and anxieties.

"There is anecdotal evidence that patients see an improvement in symptoms of long COVID once they have been vaccinated—something that we have seen in a small number of patients in our clinic. Our study will allow us to see how this biomarker changes over a longer period of time in response to vaccination."

At the moment, the team is using the tests for research purposes, but by increasing the size of their study cohort and carrying out further work, they hope to adapt and optimize the tests that can be scaled up and speeded up, able to be used by clinical diagnostic labs.

As well as developing a reliable test, the researchers hope their work will help provide an in-depth understanding of how the immune system responds to coronavirus infection—and why it triggers long COVID in some people.

Dr. Sithole added: "One of the theories of what's driving long COVID is that it's a hyperactive immune response—in other words, the immune system switches on at the initial infection and for some reason never

switches off or never goes back to the baseline. As we'll be following our patients for many months post-infection, we hope to better understand whether this is indeed the case."

In addition, having a reliable biomarker could help in the development of new treatments against COVID. Clinical trials require an objective measure of whether a drug is effective. Changes in—or the disappearance of—long-COVID-related cytokine biomarkers with corresponding symptom improvement in response to drug treatment would suggest that a treatment intervention is working.

Provided by University of Cambridge