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Thermo Fisher and the new variant

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Pinpointing new forms of the coronavirus could be vital, particularly if it mutates in response to vaccination, the company says.

Late last week the FDA warned that some of the molecular tests it has authorised for the detection of Covid-19 might be less able to pick up the new variants of the virus that are currently circulating, with the more transmissible form designated B.1.1.7 being of particular concern.

Thermo Fisher Scientific, the maker of one of the tests the FDA named, disputes that its TaqPath assay is more likely to produce false negatives when used to test a patient carrying this new variant. In fact, the group tells *Evaluate Vantage* that its test could be of great use here, since unlike almost all the other authorised assays, it appears to be able to distinguish between the B.1.1.7 variant and the wild-type virus, and thus to track the spread of this new form.

Rather than sequencing the entire viral genome, which would be a lengthy and expensive process, Covid-19 PCR tests detect one or more short stretches of viral RNA. These targets vary from test to test: Thermo Fisher's TaqPath assay identifies regions of the virus's S, N gene and ORF1ab genes, Manoj Gandhi, senior medical director at Thermo Fisher Scientific, explains. The first of these encodes the spike protein which enables the virus to bind to receptors on the patient's lungs and thereby infiltrate their cells.

The B.1.1.7 variant, first detected in the UK, carries 23 mutations compared with the wild-type, 17 of which lead to changes in protein structures. By sheer chance, one of these mutations, in the S gene, is relevant to Thermo Fisher: 69-70del, which causes deletion of the amino acids in positions 69-70 of the spike protein.

When the TaqPath assay is used on a sample from a patient with B.1.1.7, the test comes back positive for the N and ORF1ab sequences – but negative for the S gene, since the 69-70del mutation no longer matches the TaqPath's sequencing probes. This is called an S gene "drop out".

Not a bug but a feature

Mr Gandhi is adamant that this does not mean that the test will produce false-negative results, and in fairness the FDA's warning concedes this, stating that "since [the TaqPath] test is designed to detect multiple genetic targets, the overall test sensitivity should not be impacted".

But the S gene drop out in an overall positive test result would indicate, though not definitively diagnose, the presence of the B.1.1.7 variant, which is estimated to be 70% more transmissible than the wild-type. B.1.1.7 is the only emergent form of the virus whose presence the test can indicate – it cannot tell the difference

between the wild-type and the 501.V2 variant, first identified in South Africa, for example.

Still, this ability has implications beyond simply B.1.1.7's spread, Mr Gandhi explains.

"There has been some literature that says that these patients actually have higher viral load," he says, adding that "we know higher viral loads means more severe disease. There could be some diagnostic implication here. And there have been some questions about whether this might actually impact treatment."

Higher Covid-19 viral load is definitively associated with increased mortality, but the link between B.1.1.7 and viral load remains tentative. If this is borne out, Thermo Fisher's test could give an idea of patients' prognosis, with obvious implications for triage and treatment choices. As far as Mr Gandhi knows, however, there are no prospective clinical trials evaluating use of the TaqPath test in this way.

Thermo Fisher declined to say whether the TaqPath's ability to detect B.1.1.7 had led to an increase in sales of the test. But there would appear to be a competitive advantage here over the other authorised molecular tests for Covid-19, including those from diagnostics leaders such as Roche and Abbott, whose tests do not target S gene sequences.

There is one exception. The Linea Covid-19 assay sold by Applied DNA Sciences uses two regions of the S gene as its targets, one of which also results in an S gene drop out when used to test a sample from a B.1.1.7-infected person, and therefore this could, theoretically, also be used to guide treatment of B.1.1.7 patients.

Further mutations

Along with advantages, though, there is a danger. What if the virus mutates further and another of the genetic targets used by PCR tests drops out? What if they all do?

Loss of all the viral sequences a test targets would represent "a doomsday situation" for its manufacturer, Mr Gandhi says, meaning that that particular test would be rendered useless. But this is unlikely to happen, even to tests that have already experienced one drop out; Thermo Fisher is not rushing to develop a new molecular Covid-19 assay to replace TaqPath.

And there is another potential hazard on the horizon: Covid-19 vaccines. Because these induce antibodies against the spike protein, they will exert evolutionary pressure on the virus to favour mutations in the S gene that produce a different form of the spike protein able to evade vaccinated patients' immune responses.

Therefore, theoretically at least, more S gene mutations are on the way. Tests that use only S gene sequences might be at risk of becoming redundant; those that target other parts of the viral genome will be safer, though of course less likely to be able to detect any new forms of the virus that emerge.

Ultimately, assuming vaccination programmes succeed, demand for Covid-19 tests will fall. Until then, Thermo Fisher has an intriguing new use case for its test.