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Diagnostic Developers Pursue SARS-CoV-2 Omicron Assays for Surveillance, Potential Clinical Use

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NEW YORK – Diagnostic developers have quickly crafted research-use assays that can detect and distinguish the Omicron variant of SARS-CoV-2. After the US Food and Drug Administration announced on Wednesday that it will now accept Emergency Use Authorization submissions for variant genotyping assays, many of these firms will now pursue that option.

Previously, FDA had reportedly told developers that variant genotyping assays would not be reviewed for EUA, but in light of the highly transmissible Omicron variant, the agency has adjusted course.

In a town hall meeting with developers on Wednesday, FDA representatives said the agency would provide validation recommendations to interested developers of variant genotyping assays.

FDA spokesperson Jim McKinney further noted in an email, "We welcome EUA requests from test developers of high-volume genotyping assays as well as whole-genome sequencing assays."

Sequencing is the definitive way to discover and track viral variants, and is widely adopted for surveillance. But PCR-based variant genotyping can also be used to quickly detect known variants in a population. With a turnaround time of a few hours, variant genotyping could potentially offer a rapid characterization of every COVID-positive sample.

Labs have been using S-gene target failure (SGTF) to home in on Omicron, in part because some assays — like the Thermo Fisher Scientific TaqPath and others — that happen to exhibit SGTF also have EUA and are widely adopted for diagnostic testing.

However, a newly discovered sub-strain of the Omicron variant dubbed "stealth Omicron" does not contain the 69/70 deletion that causes typical SGTF. And although Omicron also exhibits N-gene target failure (NGTF) on two EUA assays, on Wednesday FDA said the use of SGTF and NGTF to definitively distinguish Omicron is "not ideal."

RUO kits at the ready

Assay developers such as Roche, Eurofins, Seegene, Aldatu, DiaCarta, EliTech, and many others have already launched research-use variant genotyping tests for Omicron surveillance.

Olfert Landt, the founder of TIB Molbiol, said that his firm — which is a newly acquired subsidiary within the Roche Diagnostics division — has sold more than 150,000 Omicron-specific assays in the past 10 days to more than 120 labs. And overall, the firm has sold 5.9 million PCR assays since December 2020, he said.

The Omicron tests use the firm's VirSNiP technology and can be combined with SARS-CoV-2 diagnostics testing to provide simultaneous diagnosis and variant identification by essentially splitting a sample into two reactions in a high-throughput testing system.

The assays work with Roche diagnostics systems, but also with other qPCR instrumentation, Landt said.

Tib MolBio is able to spin out new variant tests using its VirSNiP chemistries quite rapidly, and Landt noted that in the past year the firm has developed and marketed more than 50 different assays.

However, the dominant variants of the virus can shift quickly, so "the lifetime of VirSNiP assays is sometimes only weeks," he said, noting as well that this window of utility may be "much shorter than typical IVD registration procedures."

The tests can nevertheless be "quite useful" from an epidemiology and contact tracing standpoint, he said, even though they are not currently used for clinical decision making.

Similarly, Eurofins Technologies' IVD assay kit development subsidiary, Gold Standard Diagnostics, or GSD, has already launched an Omicron-specific test, called the GSD NovaType Detect + Select K417N SARS-CoV-2 test kit.

According to Heidi Bursen, senior director of product development and innovation at GSD, the test detects the N1 and N2 gene targets of the virus as well as the K417N mutation that is thought to be specific to the Omicron variant.

The kits are research-use-only and are offered globally in Eurofins labs as well as to external customers, Bursen said in an interview.

However, the diagnostic kit the firm submitted for EUA last year languished in the queue at FDA, so Eurofins currently only offers its assays as EUA lab-developed tests in US Eurofins labs.

In terms of surveillance, "Until Omicron, the strategy in the US was to go directly for sequencing," Bursen said, "But there is now some interest from the government ... so we will try to engage with the US government again."

The SGTF workaround has been used by US public health labs as well as in some European countries, but Bursen said Omicron's stealth lineages will likely be missed by this approach.

"Our rationale was to use a specific test that can be used for detection of Omicron," she said.

The team already had a singleplex assay for the K417N mutation, and so it combined that with the SARS-CoV-2 screening assay into a single-tube reaction.

Depending on the course of the pandemic, the product may be CE IVD marked, Bursen said.

But, "If there are changes in the Omicron sequences, maybe at some point it doesn't make sense anymore to make a CE product out of it," she added.

To this end, the firm queries the GISAID database daily and runs *in silico* analyses of its tests using the 3,000-and-counting Omicron sequences uploaded.

Back when the Alpha variant was a concern, a clinical utility argument for variant testing was made because one of the monoclonal antibody treatments was less effective. With Omicron's current doubling time of about three days, waiting a week for whole-genome sequencing is not ideal, and

Bursen said PCR-based methods could have an advantage in controlling the spread, perhaps through patient isolation and contact tracing.

EliTech has also recently launched a test, called the SARS-CoV-2 Extended ELITe MGB Kit, that detects and distinguishes the Alpha, Beta, Gamma, Delta, and Omicron variants in a single multiplex PCR using melt curve analysis. The research-use test can be run on the firm's ELITe InGenius system as well as on the ABI 7500 FDx, QuantStudio 5, and Bio-Rad CFX-96, the firm said in a statement.

Enabling chemistries and workflows

Still other developers, like Aldatu, DiaCarta, and Seegene have developed variant genotyping assays using unique proprietary chemistries as well as rapid assay development pipelines.

Aldatu's pan-degenerate amplification and adaption, or PANDAA, chemistry, for example, was developed specifically to detect viruses that frequently mutate, like HIV and Lassa fever.

According to the Iain MacLeod, cofounder, CEO, and CSO at Aldatu, the PANDAA technology can compensate for primer/probe mismatches, so it can detect SARS-CoV-2 despite any changes in the genome.

"You might call it an insurance policy against unknowns, because you don't have to change the design of your test in the future to compensate for changes," MacLeod said.

Using the same technology, Aldatu can also rapidly differentiate variants, he said, and the firm recently launched its PANDAA qDx SARS-CoVar Variant Genotyping Test Kit for research use.

"We are able to detect and differentiate 12 different variants," MacLeod said, specifically through combinations of six mutations in the S-gene, including K417N, in an assay that is run in two reactions. Using 96-well plates, 46 samples can be characterized "in a few hours," MacLeod said.

The firm's initial SARS-CoV-2 assay was also developed rapidly and was adopted early on in the pandemic in sub-Saharan Africa, where the firm has existing relationships. Its test was also among the first to be used in the US, MacLeod said, with hospitals in Boston first using it on March 18, 2020.

Aldatu submitted its test for EUA in May of last year but was finally informed that the FDA had declined to review its application in March of 2021.

"We were told that our adaptive PCR technology — which ensures robust SARS-CoV-2 detection as new variants arise — wasn't a priority and would have 'limited impact' on testing," MacLeod said, despite the fact that the assay doesn't need to be updated for new variants due to the qualities of the PANDAA chemistry.

Nevertheless, the firm is now considering pursuing an EUA for its variant test, MacLeod said.

In the meantime, it also offers its variant detection assay as a kit and as a lab testing service as it continues to work on viral hemorrhagic fever assays.

Aldatu is also currently developing a pan-coronavirus multiplex test that can detect and distinguish all known alpha and beta coronaviruses, such as SARS-CoV-1 and CoV-2, MERS, and the coronaviruses that cause the common cold. A pan-target positive result using this assay that is also negative for the known viruses targeted would therefore signal the presence of something novel, potentially a "disease X," that could then be prioritized for sequencing.

Diagnostic developer DiaCarta, meanwhile, uses a unique chemistry called XNA that it claims can dramatically improve the specificity of a PCR assay.

Ramanathan Vairavan, senior VP of commercial operations at DiaCarta, said the firm had already developed its SARS-CoV-2 Variant Detection Kit when Omicron was discovered, and quickly noted that its kit would likely detect Omicron through a unique combination of mutations N501Y, T478K, and K417N.

Overall, DiaCarta's synthesis of XNA and finalizing of primer and probes took one week, Vairavan said, and then it took another two weeks to optimize the assay and have it validated in the firm's CLIA lab as an LDT.

The firm's primary target customers for its variant test are now national and state labs that perform surveillance, and the firm emphasizes that the cost per sample of its PCR-based method is about one fifth that of sequencing.

But there may also be a potential diagnostic application, for example if it turns out certain vaccines are less effective against Omicron, Vairavan said.

So far, "There has been a lot of interest in international markets for the variant detection test," he said.

DiaCarta is now generating data for FDA EUA submission of its variant test and will be submitting soon.

Seegene was also able to quickly develop a test — called the Novaplex SARS-CoV-2 Variants VII assay — that is able to detect Omicron and stealth Omicron as well as other known variants.

According to Helen Roberts, president of Seegene Technologies, the firm developed its Omicron-specific test in two days, then validated it *in silico* and through preliminary lab analysis in two weeks.

Such rapid multiplex assay design for tests with at least three mutations is unique in the industry, she said, noting that these are RT-PCR tests and can report Ct values for each target.

Bruno Larida, Seegene's VP of marketing, noted that the Variant VII assay detects Omicron and stealth Omicron through combinations of the 69/70 deletion, the E484A and N501Y mutations, and the presence of the RdRp gene.

Roberts said that Seegene's SARS-CoV-2 variant assays have been rolled out on a national scale to screen for Omicron "before, or in lieu of, NGS," in Indonesia, Israel, Wales, Czech Republic, and Chile.

In the US, Larida said that CardioPath Laboratory in Miami used Seegene variant testing to find the first local case of Omicron.

There are also healthcare systems in the US using Seegene tests for reflex testing and epidemiological tracking of variants, Roberts said. She was not authorized to name the health systems, but said one used the Seegene test to find a suspected case of Omicron that was subsequently confirmed by sequencing at a state public health lab approximately two weeks later.

A lack of reimbursement for variant testing remains a constraint, Roberts said. However, there is a possibility that the economics may change should variant genotyping finally garner EUA or become clearly clinically necessary.

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