Variants, vaccine efficacy, and the tests labs need

Sherrie Rice

July 2021—For SARS-CoV-2, there has to be a plan to sequence locally and collaborate globally, and public health must recognize that hospital-based laboratories have a part to play, says Glen Hansen, PhD, D(ABMM), medical director of microbiology and molecular diagnostics at Hennepin County Medical Center, Minneapolis.

Dr. Hansen

Speaking in a CAP TODAY webinar on variants and their detection, Dr. Hansen said diagnostic manufacturers have shown that variant assays can be brought to market for clinical laboratories. "And we need to support them so that when a clinically valid mutation comes around that we need to look for, we have the chance to do it," he said in the April 28 webinar made possible by a special educational grant from Seegene Technologies. (Dr. Hansen's full comments, and the accompanying presentation by Valerie Ng, MD, of Alameda Health System, are at www.captodayonline.com.)

The current contemporary COVID-19 variants are B.1.1.7 (U.K.), B.1.351 (South Africa), P.1 (Brazil), and B.1.427/B.1.429 (California). To examine variants in the field, the sera of those who are vaccinated and have natural exposure is exposed to the virus, "and we get complete effective neutralization like we see with the U.K. variant B.1.1.7. There is no effect of B.1.1.7 on vaccine escape," said Dr. Hansen, who is also associate professor of pathology and laboratory medicine and of medicine and infectious disease, University of Minnesota Medical School.

"And then we see things in between with the Brazilian and California variants, and we do see a sixfold reduction in sensitivity of neutralization with the South African variant. But the efficacy of the vaccines is so high that we're still struggling to identify what a sixfold reduction in sensitivity would mean clinically," he said.

Spike protein mutations equal COVID-19 variants. Spike proteins are made of three equal parts called protomers, and when the spike opens, it lends itself to a more transmissible virus because it can bind the cells easier. "That allows more binding of the virus to cells, higher viral titers, higher amounts of virus that can be spread," he noted.

A number of mutations have emerged, one of which is N501Y, "which we've seen as a mutation in the spike protein that allowed the native conformation to open. We've also seen N-terminus domain deletions, complete deletions in sections of the spike receptor protein. This is what public health is looking for."

Mutations at L452R and E484Q have been known for some time. There's a leucine to arginine substitution at L452R-carrying virus, which is the same variant found in the California variant. "We know from studies that this mutation shows a greater affinity for the spike protein to enter the cell," Dr. Hansen says. Many of the contemporary variants of concern have an active mutation at the 484 site. "The substitution of glutamic acid for lysine typically reveals a mutation called E484K."

The variants in India are very different, and the differences seen are substitutions of glutamic acid for glutamine. "Glutamine is a polar uncharged mutation, and what we're seeing with the substitution of glutamic acid for lysine is the addition of a positive charge conversion. This is the first time we've seen this at this receptor binding site, and this is of concern."

When U.K. B.1.1.7 was identified, Dr. Hansen said, "we saw increased risk of hospitalization within 14 days of

sampling for B.1.1.7 versus nonvariant cases" (n=63,609 sequences). And the case fatality rate for confirmed/probable B.1.1.7 changed—2.6 percent. Based on preliminary U.K. data, the relative risk of death is 1.65 percent for B.1.1.7 versus a matched cohort of nonvariant cases. "All different numbers than what we saw with the virus that was initially described coming out of Wuhan." Importantly, he said, there's no evidence for higher rates of reinfection, and dramatic changes in the neutralization of the virus relative to the vaccines have not been seen.

"To measure these, we take neutralizing antibody from patients infected with the virus, challenge it with the variants, and see what we have." The big caveat about these experiments, Dr. Hansen said, is what is not present in infected serum, which are the T cells, and in many cases the plasma cells. "We do not have the ability to readily assess the cellular response in these type of experiments." It's important, he said, because it's been known from the start that the answer to protection for COVID-19 is not completely dependent on antibody. "If it had been, then all of the discussions about transferring convalescent plasma would have had a different approach, and in fact this was borne out clinically. Early in the outbreak, we saw patients who unfortunately succumbed to the virus in our health care institutions, and they had overwhelming amounts of antibody, yet the people who recovered from infections had smaller amounts. So it raises the question: What provided the protection that allowed some people to fight off infection naturally? We now know almost unequivocally that there is a cellular response to COVID-19."

Faster spread due to increased transmissibility is a consequence of the variants, but the central question is whether the variants can evade diagnostic tests and the immune system. How the variants affect diagnostic platforms has been the focus of much discussion, he noted, adding, "We'll be looking for that going forward. We're looking also at the decreased susceptibility of therapeutic agents. I firmly believe that the next year will bring a number of therapeutic responses to COVID-19, so we'll be looking to see how the variants affect those, and we're going to look at the evasion of natural or vaccine immunity."

Are variants likely to affect vaccine efficacy? Novavax is a new protein-based vaccine that has been studied in the U.K. in trials of about 15,000 specimens, Dr. Hansen said. Overall efficacy was greater than 89 percent, where more than 50 percent of the cases were due to the U.K. variant. This same vaccine in smaller numbers (4,400) was challenged in South Africa, where 92 percent of the confirmed cases were the South African variant, and efficacy was 60 percent. "Why are the numbers different? We don't know, and this is something we're looking at," he said. "All of the discussion around the variants, although we focus on diagnostics, is, 'Will we find a variant that will escape the vaccine and allow the virus to enter cells in the presence of the vaccine or more specifically in the presence of antibodies?'"

Hennepin County Medical Center has seen a decrease of eight years in the average age of admission and an increase of 125 percent in admissions among those 20 to 35. "So if you're looking for the clinical impact of variants, longitudinal data would suggest that we are seeing differences in the epidemiology of where we start to see COVID infections."

One approach to this is to sequence the virus on hospitalized patients, which is what the public health response has been, with the support of laboratories to provide samples to sequence. "And there are now a number of new tests available to labs," one of which is the Thermo Fisher custom TaqMan assay, which allows allelic discrimination of some of the variants. Another is the Roche Cobas SARS-CoV-2 Variant Set 1 that looks for targets N501Y, E484K, and del69–70, which can be run on the 6800 and 8800 systems. (There's no positive control, he notes, but he said Twist Bioscience has good controls for variants.) "The idea with tests like this is that a lab can screen. We can screen in high numbers fairly easily, identify those variants, and transfer those variants on to public health."

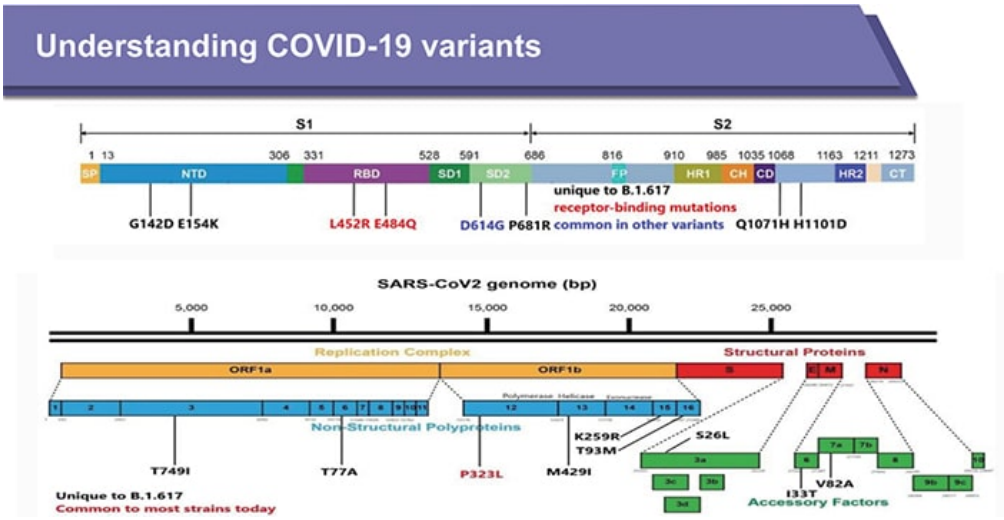
SmartGene's modules for SARS-CoV-2 are another example, Dr. Hansen said, "and we are strong partners with SmartGene in our lab as well." This is France's solution for decentralized sequencing and national surveillance, he said, and it supports Sanger and next-generation sequencing. "This is software you can buy that will allow whole genome assembly and lineages. They have a great functionality report to upload to the databases, and this is something you can do in your lab if your lab is familiar with next-generation sequencing or Sanger methods."

Seegene has three assays: Master, Variants I, and Variants II. In 48 hours of variant testing using a Seegene assay

at Hennepin, Dr. Hansen said, 83.1 percent of all positives were a variant of some type: 65 percent were B.1.1.7, and six percent were a combination of the Brazilian, Japanese, and South African variants.

What will be done with variant data?

"There's no question that they're going to filter into booster strategy," he said. "We also know that interacting with our plasma cells will be an answer, to stimulate the immune system to produce specific antibodies." Another strategy would be a third shot of a current vaccine that would increase the antibody affinity for what it is hoped can be established.



But there's the always-present question of who pays. "Variant testing at this point is not covered, to my knowledge, in CMS pathways," Dr. Hansen said. He reminds public health authorities, he said, that there is $1.7 billion under the American Rescue Plan, and public health offices need to understand the value of partnering with local hospitals. "It's one of the lessons learned from the outbreak. Public health did not do a good enough job of engaging testing on the ground with local hospitals, and we need to learn from that. So is there an opportunity for public health to help laboratories help screen some of these samples to move them on to public health agencies?"

If there is no clinical impact in terms of treatment or management, he asks, why do it? One of the lessons learned in the outbreak is the tremendous need for preparation, he said.

"The CDC office was opened in 1946 exactly for what just happened with COVID-19, and we fumbled it. So you can look at these assays and say, 'How useful are these assays? There's a new variant coming every week. As soon as I validate, it's going to be out of current pace.'

"The value of the commercial variant assays," he said, "lies in showing us how these assays can be produced and made available to labs across the country, hopefully on a much smaller scale than what we experienced initially."

Variant assays offer a "road map," Dr. Hansen said, of how to develop and apply the assays so that if and when a variant arises that has an impact on clinical care beyond transmission rates, labs can be prepared.

"A number of diagnostic colleagues have now shown us these assays are possible, and this is the message we can take from variant assays today."

Sherrie Rice is editor of CAP TODAY.