Clinical Laboratory COVID-19 Response Call

January 11, 2021

Agenda

- **Welcome**
  - Jasmine Chaitram, CDC Division of Laboratory Systems (DLS)
- **OneLab Network Overview**
  - Senia Wilkins, CDC Division of Laboratory Systems (DLS)
- **Preliminary Data from BinaxNOW Antigen Testing**
  - Jessica Prince Guerra, CDC Laboratory and Testing Task Force
- **Vaccine Effect on Serology Testing**
  - Natalie Thornburg, CDC Laboratory and Testing Task Force
- **Surveillance Testing for non-CLIA Pop-Up Labs**
  - Amy Zale, Centers for Medicare & Medicaid Services (CMS)
- **FDA Update**
  - Tim Stenzel, U.S. Food and Drug Administration (FDA)

JASMINE CHAITRAM: Hey everyone. I'm Jasmine Chaitram. I am the Associate Director for Laboratory Preparedness in the Division of Laboratory Systems. Thank you for joining the Clinical Laboratory COVID-19 Response Call. The Division of Laboratory Systems has been hosting these calls since March. And if you've been with us since March, you already know that.

And you probably already know that the Division of Laboratory Systems has been serving as a liaison and a communication and coordination piece at CDC with the clinical and public health laboratory community. We were doing this before COVID in topic areas such as quality and safety, training and workforce development, informatics, data and biorepository science, as well as preparedness and response. And since COVID-19 has arrived, the Division of Laboratory Systems has been working with laboratories on response activities and hosting these clinical laboratory calls. It's just one of the things that we do.

I'm showing today's agenda. We've got a number of speakers. And I will try to announce when they have slides and when they don't. The agenda was sent out through our Laboratory Outreach Communication System, which is LOCS. And we use that to communicate by email with all of our clinical laboratories and our partners. If you don't have access to LOCS, or you do not receive emails directly from us, you're welcome to sign up by sending us a communication at LOCS@cdc.gov.

Before we get started today, I do have a couple of announcements I wanted to share with you. The first is that Admiral Giroir has posted a video on YouTube which talks about an updated national testing strategy. It's about 30 minutes, so if you want to check out that video, we

provided the link to it here. And this will be in our slides, which we post after the calls to the DLS Preparedness Portal, which I will show in a second.

But here are also some useful links that we include in our slides every time we do one of these calls. So that's quick access to information that you might be interested in. Here is our DLS Preparedness Portal. And this is where you will find the transcripts as well as the slides and the agendas from previous calls. So any links that you want to get access to, any slides, they'll be posted here. Also, our calls are scheduled every other Monday.

And so our next call will be on January 25 from 3:00 to 4:00 PM. And we continue to want to get your feedback about training and workforce development needs. So you can email us at LabTrainingNeeds@cdc.gov.

And finally, I wanted to mention how to ask a question. There is a Q&A box or button in the Zoom webinar system. And please use that to submit your questions to us. Do not use the chat button. We would like you to, if you're comfortable enough, to include your email address and your name in your Q&A when you submit your question to the Q&A section. And that allows us, if we're not able to answer your question during the call, to follow up with you and to provide an answer later on.

So we do appreciate you providing those emails. We will try to answer as many questions as we can during the call. But because of the time and the number of questions that we get, sometimes it's not possible to do that. So we appreciate your patience, and we will try to answer your call either-- sorry, answer your question, either by email or on a future call. But we do appreciate you submitting those questions. It does help us to shape our agenda to understand what it is that you're looking to have information about.

And then a couple of other things. If you're the media, please contact CDC Media Relations at media@cdc.gov. And if you're a patient, please direct your questions to your health care provider. And with that, I think we're ready to move into our agenda. Our first speaker is actually also from the Division of Laboratory Systems. It's Senia Wilkins. And she's going to be talking about the OneLab Network and giving a brief overview of that. Senia?

SENIA WILKINS: Thanks, Jasmine. Hi, everybody. It's been a couple of months since I've last spoken to this group, so thank you for having me again. I wanted to give a really quick update-- hopefully it won't take too long-- on our new initiative called OneLab, of which a big component of that will be standing up the new network, which I'm going to briefly talk about. You'll probably receive correspondence around the network from various channels, so you might see it more than once. I hope you see it more than once, actually. And so let's go ahead and go to the next slide.

So our long-term goal with OneLab-- I think I alluded to it months ago when I first talked to this group. It just didn't have a name at the time, so you might not recognize it. And it's a lot more structured and fleshed out, strategically speaking. So our long-term goal with this initiative is to

establish a sustainable learning community of clinical laboratories, public health laboratories, and CDC to collectively support rapid large-scale emergency responses. So, next slide. Thank you. Great. So in other words, we want to-- laboratory education and training partners, we want them to come together as one lab and to deliver a unified response to COVID-19 training needs-- specific COVID-19 training and education needs, but also long-term to all emergency responses. So that's the long-term vision.

In the short term, we have a couple objectives that we want to work on this year, the first of which, as I mentioned, is to stand up the network. After the network is stood up, we want to deploy a rapid needs assessment and then prioritize what new education and training services or resources align and help address some of the needs that were discovered under that second bullet. Then we want to work together to get these in the hands of the intended target audiences through wide-scale dissemination strategies, whether it's through digital platforms or existing channels.

We'll work together to identify those, or if we need to build something new, and then ultimately linking to the long-term objective. We do want to do everything we can throughout this process to keep in mind that we want this to be an ongoing learning community. So, next slide.

So who should join? So representatives with responsibility for education and training within political laboratory professional organizations, manufacturers, large commercial laboratories, and large hospital systems. So could be hopefully folks from within your organizations or networks that have a responsibility for education and training.

Or it can be-- we're not sure. It could be individuals from outside our traditional networks and organizations, but that still have a responsibility to provide education and training resources to the clinical laboratory audience. So that's why we're casting the net pretty wide-- to make sure that all those that fall under this category have the opportunity to learn about this initiative and sign up for it.

So the way you sign up is you go to cdc.gov/OneLab. It'll recap some of the information I just shared with you all today. And it's also a quick and easy email, and yes, I want more information to sign up, after which an invite will be sent for the first kick-off meeting. And then you'll receive even more information at the kick-off meeting. So that is it. If you have any questions, you can email OneLab@cdc.gov. And thank you in advance for sharing this information with your colleagues. Thanks, Jasmine.

JASMINE CHAITRAM: Thanks, Senia. We did get one question I think for you. It says, what about the small labs for the training? So I don't know if that's-- what about small labs participating?

SENIA WILKINS: Yes. There's no requirement on the size of your lab or location of the lab. So if you have someone that has a responsibility for training small labs or within a small lab, send them over to the web page so they can sign up.

JASMINE CHAITRAM: OK, great. Well thank you so much for joining us today.

SENIA WILKINS: Great. Thanks for having me.

JASMINE CHAITRAM: OK, great. We're going to move to our next speaker. It is going to be Jessica Prince-Guerra from the CDC Laboratory and Testing Task Force. And she's going to be talking about preliminary data from the BinaxNOW™ Antigen Testing.

JESSICA PRINCE-GUERRA: Great, thank you, Jasmine, and welcome, everybody. So today I'm going to be talking about a preliminary data from a BinaxNOW™ antigen testing evaluation that was conducted in collaboration between CDC, the Arizona Department of Health, and the Pima County Health Department. Next slide, please. Next slide, please.

So this evaluation of the BinaxNOW™ antigen test was conducted in collaboration with Pima County, Arizona in two community-based testing sites. Individuals were enrolled in the evaluation between the ages of 10 and 95, and paired samples were collected by a health care professional. First, a bilateral nasal swab was collected for the antigen test, followed by a bilateral nasopharyngeal swab for a real-time RT-PCR test. You can have testing with the BinaxNOW™ antigen test and real-time RT-PCR was conducted.

The BinaxNOW™ antigen test was conducted on site. And the real-time RT-PCR was conducted at a commercial laboratory that was contracted through Pima County. And it's important to note that the real-time RT-PCR assay was divided between different assays. So 75% of the samples were run using this PT assay, and about 25% of the samples were run using the Fosun real-time RT-PCR assay. And 274 samples that were positive from either test have been tested by viral culture at the labs here at CDC. Next slide, please.

In the evaluation, 3,419 participants were enrolled, and they were aged 10 to 95 with a median age of 41. And of the 3,419 participants, 76% were asymptomatic, and 24% had one or more symptoms that was consistent with COVID-19. There was 3/4 of the individuals self-reported their race as white, and nearly 1/3 self-reported their ethnicity as Hispanic or Latino.

Among asymptomatic persons in the evaluation, 1.9% were positive by the antigen test, and 4.7% were positive by real-time RT-PCR. Among symptomatic persons, 13.7% were positive by the antigen test, and 21.3% were positive by real-time RT-PCR. Virus was recovered from 96 out of 274 samples that were positive by either test and that were sent to CDC for viral culture. Next slide, please. Next slide, please. Thank you.

So when we look at the BinaxNOW™ test performance compared to real-time RT-PCR divided between symptomatic and asymptomatic individuals, we find that the BinaxNOW™ sensitivity

among symptomatic individuals with 64.2%, while specificity was 100% with no false positive antigen results identified. The positive predictive value was 100%, and the negative predictive value was 91.2%.

Among asymptomatic persons, the BinaxNOW™ sensitivity was lower than in symptomatic individuals at 35.8%. Specificity in this group was also lower at 99.8%, with four false positive antigen test results identified. Positive predictive value was 91.7%, and the negative predictive value was around 97%. Next slide, please.

So when we look at the results by viral culture and by real-time RT-PCR CT counts, as shown on the slide, of the 274 samples that were positive for either test and sent to CDC for viral culture, 96 of them or 35% were positive by viral culture. And among concordantly positive samples, so those samples that were both antigen and real-time RT-PCR positive, 85 out of 147 or 57.8% were positive by viral culture. And interestingly, among false negative samples by the antigen test, 11 out of 124, around 9%, also had culturable virus detected. And none of the false positive samples that were sent for viral culture had culturable virus.

And in the figures to the left, we're plotting the n1 cycle threshold value on the y-axis, divided between antigen-positive and antigen-negative samples among symptomatic and asymptomatic individuals. And the colored dots-- so the red color dots refer to culture-positive samples. And the black refers to culture-negative samples.

And what you can see from this figure is that among samples that are antigen-positive, they have a lower Ct) value than those samples that are antigen-negative, indicating that the antigen test is picking up samples with higher viral RNA loads. And the antigen-positive samples have a higher proportion of the samples that were culturable by virus. But there was still virus that was culturable in the antigen-negative group in both asymptomatic and asymptomatic groups. Next slide, please.

So when we look at the antigen test sensitivity, only in those samples that had positive viral culture, we find that the test sensitivity increases among both symptomatic and asymptomatic individuals. So in symptomatic individuals, the test sensitivity was 92.6%. And in asymptomatic individuals, it was 78.6% in those samples that were positive by viral culture. Next slide, please.

So in summary, the sensitivity of the BinaxNOW™ antigen test was lower in asymptomatic than in symptomatic persons, but specificity was high among both groups. The sensitivity of the test was also higher among viral culture-positive samples. However, some antigen test negative samples also had culturable virus.

Thus, symptomatic persons who receive a negative antigen test result should receive confirmatory testing by a nucleic acid amplification test. And despite the limitations in test sensitivity, the faster turnaround time of this antigen test can limit transmission by more rapidly identifying infectious persons for isolation. And with that, I'd like to thank Jasmine and everyone for listening. And I'd be happy to take any questions if there's time.

JASMINE CHAITRAM: Jessica, sorry. I was double-muted. We do have a couple of questions for you. Thanks for the presentation. The first question is, which real-time PCR assay was used for the study?

JESSICA PRINCE-GUERRA: Right. So there were two different assays that were used. 75% of the samples were run using the CDC singleplex assay, and 25% of the samples were run using a Fosun assay. And both of them have similar limits of detection.

JASMINE CHAITRAM: And what was the Ct cutoff for that PCR assay?

JESSICA PRINCE-GUERRA: So for the CDC assay, it's 40 cycle thresholds. And for the Fosun assay, it's 36. And that's why we didn't combine them on the same Ct graph, and we only showed the CDC samples.

J**ASMINE CHAITRAM**: Could lower sensitivity of antigen-- hold on one second. I just lost it. Oh, here we go. Could lower sensitivity of antigen tests be partly due to different types of specimens-- nasal versus nasopharyngeal?

JESSICA PRINCE-GUERRA: Yeah, that's certainly a possibility. And there are some data that will be coming out soon in which this-- the BinaxNOW™ is compared in a asymptomatic college setting in which a nasal swab was used for the PCR. And so they also observed lower sensitivity. So it certainly could impact the results. But there's also some data suggesting that even with a nasal, the nasal swab sensitivity is lower.

JASMINE CHAITRAM: Great. All right, thank you so much. We're going to move to our next speaker today. I do appreciate you being with us, Jessica. If you are still on the line when we get towards the end of our agenda, if there are additional questions, I'd love to send some more to you.

Our next speaker is going to be Natalie Thornburg from the CDC Laboratory Testing and Task Force also. And she's going to be talking about the vaccine and the effect on serology testing. Natalie?

NATALIE THORNBURG: Hi, Thanks. Yeah, so I'm going to go through and talk a little bit about serology testing and how that might change after introduction of the vaccine. Go ahead, next slide. So there are currently 59 serological tests that have received FDA EUA authorizations that detect antibodies against SARS-CoV-2.

Those include assays that are just qualitative and give you a yes/no answer or semi-quantitative-- those that give you some sort of quantitation output. And they target the spike protein, portions of the spike protein, or the nucleocapsid protein. We have a collaboration with FDA, NCI, and NIH that has independent evaluation of tests, where they have generated panels of positive and negative sera, and then have evaluated many tests. And together, we've evaluated 85 different tests to validate those tests. Next slide.

So just a little bit of virology information to remind you of why these proteins are relevant. So there are two main targets for the antibody tests, those that detect antibodies against the spike protein, which is shown in red, and those that detect the nucleocapsid protein. So the spike protein is the protein that is in all vaccine products. And all of them only have the spike protein, at least the ones that have received EUA authorization and that are in on the late phases of clinical trials.

Some tests have the entire ectodomain or the full spike. Some tests detect just a portion of the spike protein or S1. And some detect the receptor binding domain, which is the part of the spike protein that binds to the cellular receptor, ACE2. And then other ones like, I think, Abbott and Roche, detect antibody tests against the nucleocapsid protein.

And then some are multiplex in that they detect antibodies against both S and N. And they use different secondary antibodies. Some detect any Ig. Some are IgM, some are IgG, and then some are IgG-IgM. Next slide.

All right, so how the isotypes are relevant-- the classical model of seroconversion indicates that IgM comes up very early during infection. And then as it wanes, IgG comes up a little bit later. We've learned through the spring and through the summer that that's not necessarily true for SARS-CoV-2.

So this is one paper that was published in Nature Medicine. And now there are numerous papers that corroborate this data and show the same thing-- that in some patients, IgG and IgM can come up-- one can come up first, the other one can come up first, or they can come up simultaneously. So IgM and IgG cannot necessarily be used the way it had been used against other infectious diseases, and that if you just detect IgG and not IgM, it doesn't mean that this is an infection that happened long ago. That can happen during the acute phase of infection. And so one should not overinterpret isotype responses to this infection. Next slide.

All right, so we know now that we're 10 months into this pandemic. And so that there are numerous papers that have been able to collect sera from individuals six to eight months after infection. This is just one of those infections or one of those papers that shows pre-pandemic controls, and then shows IgG on the top panel, IgM in the middle panel, and IgA on the bottom panel and shows detection of serum antibodies against the virus over time.

And you can see waning of serum IgM and IgA. Over the course of this study, they went out to about 120 days. This one only looked out four months. And IgG lasts a little bit longer. But there are some sporadic specimens that you can still detect some IgM or IgA four months out.

So there's waning over time, but still detectable at four months post-infection. Our own group and then several other groups have looked out to eight months, and still you see waning between symptom onset and six to eight months. But antibodies can still be detectable even out that far. All right, next slide.

How does that compare to waning immunity after vaccination? Well, this was published in The New England Journal of Medicine and looks at the durability of response after vaccination with the Moderna vaccine. And it looks at 34 individuals. And they see very similar results. So they looked at an RBD. So an RBD ELISA, so part of the spike protein on the top panel, or a pseudovirus neutralization assay, so functional antibodies.

And they see very similar results. This is about the same time frame as that previous slide-- about 120 days or about four months. And they see some waning of binding and neutralizing antibodies, although still above the limited [AUDIO OUT] at four months. All right, next slide.

So what does that mean for in summary of serological testing after vaccination and natural immunity? Well, one, a reminder-- vaccine products use the spike ectodomain. Therefore, any antibody test that detects antibodies against the full spike, S1, or RBD should detect antibodies against either natural infection or vaccination.

So if an individual is getting an antibody test against using a spike product, you won't necessarily be able to know just from that antibody test whether it is from vaccination or from natural infection. Antibody tests that target the nucleocapsid protein should not become reactive after vaccination. All vaccine products that are being used currently only have the spike protein.

So if an individual is positive for an antibody test with a nucleocapsid assay, that should indicate natural infection. Antibodies after natural infection and vaccination very similarly seem to decrease over time, and IgG can persist, though the waning or the presence of any specific isotypes will not differentiate between vaccination and natural infection. And I believe that it's my last slide. So if I have some questions, I can answer them.

JASMINE CHAITRAM: All right, thank you so much, Natalie. There are a couple of questions. The first one is, what is the process for testing people for the coronavirus assay once they have received the vaccine-- specifically, when they have developed COVID-like symptoms down the road?

NATALIE THORNBURG: So I don't know if we're going to make any specific recommendations about getting antibody testing. But if they've already had the vaccine, and they've already had the vaccine, and then they get symptoms, utilizing any test that targets the spike won't give you any answer. You will get a nonanswer from that. You won't be able to tell if that was from their vaccination or from an infection. So if you truly want to use an antibody test to determine if that person has been infected, you will have to use one that targets the nucleocapsid.

JASMINE CHAITRAM: OK, thank you. The next one says, we are running the Roche anti-SARS-CoV-2 semi-quantitative assay. What is the CDC'S recommendation in the way of post or pre, post-vaccination testing to confirm seroconversion for the COVID vaccine?

NATALIE THORNBURG: OK, so I believe the Roche essay-- I don't have all the assays memorized. But I believe the Roche assay is nucleocapsid. So that assay would not detect an antibody response from vaccination, if I'm correct that it's nucleocapsid.

JASMINE CHAITRAM: Let's see. Does the CDC plan to compare methods and their results in post-vaccinated individuals?

NATALIE THORNBURG: Do you mean-- I guess I might need some more clarification. Does CDC compare methods and their results in post-vaccination? If they're asking if we're going to look at the magnitude of a response in natural infection versus vaccination, yes, we are going to try to do that and make that publicly available whenever we-- those studies are done and completed.

JASMINE CHAITRAM: All right, let's see. Is the CDC quantitative serology assay available commercially?

NATALIE THORNBURG: No, we do not personally have any commercially-- or have not developed any commercially available antibody assays. And I do not believe we plan to do so.

JASMINE CHAITRAM: And are the antibodies post both injections or just the first?

NATALIE THORNBURG: It should be a prime and a boost. So you should get antibodies developing about two weeks after the prime, the first injection. You should start getting antibodies. And then after the second dose, it should go even higher. And I think they max about seven to 10 days after the second dose.

JASMINE CHAITRAM: And I'm not sure if you know all these answers because I know there are different task forces that are working on different aspects of the vaccination rollout and recommendations. So the one question I have here is, will CDC change the reinfection immunity period from three to six months?

NATALIE THORNBURG: Oh, I don't know that. Yeah, I don't know that answer.

JASMINE CHAITRAM: All right. Let's see.

NATALIE THORNBURG: Someone corrected me. The Roche test is a spike. The Roche test that they asked earlier is a spike-focused test. And so that could be used to test vaccine antibody response. So I'm correcting my earlier answer. Thank you to the person.

JASMINE CHAITRAM: Thank you for doing that. And I think some of these are similar. Will the CDC be recommending post-vaccination testing for IgG spike-based antibody seroconversion? I feel like we've asked that already, but.

NATALIE THORNBURG: No. I don't think, logistically speaking, it would even be possible to test every single person who receives the vaccination during the vaccine rollout for the next six months.

JASMINE CHAITRAM: And what are the best times-- best time points to check for antibodies to assess vaccination response?

NATALIE THORNBURG: About two to three weeks after the second dose.

JASMINE CHAITRAM: All right, thank you, Natalie. I'm going to move to the next speaker just so we can get some of our other topics in. But if you're also still on the line, I may come back and ask you a few more questions before-- if we have enough time before our time ends for this call today. And thank you so much for being with us.

So our next speaker is going to be from CMS-- a speaker that we've had many times. It's Amy Zale, and she's with the Centers for Medicare & Medicaid Services, in case any of you out there don't know what CMS stands for. And she's going to be talking about surveillance testing for non-CLIA pop-up labs. Amy?

AMY ZALE: Thanks, Jasmine. Thanks for having me back. I appreciate it. I hope everyone's doing well. Thank you for everything you're doing out there. Everyone appreciates the tough job that you're doing.

CDC had asked me to hop on the call today to talk about the pop-up labs offering surveillance testing, which means that they are not CLIA-certified, and they are not using an assay that has an FDA EUA. And they're being offered to individuals who would receive test results directly.

Apparently, these labs are marketing themselves to schools and businesses as low-cost alternatives to official testing. And we just wanted to make sure that we came on and made clear that if any entity is doing any COVID testing, and they are reporting a patient-specific results to the individual who was tested, then they need to have a CLIA certificate. And so we're hearing a lot of people who are calling what they're doing surveillance because surveillance testing, as it's known in aggregate, or patient-specific results are not returned to the patient or to the provider, is known as surveillance testing. But just because it's called surveillance testing doesn't necessarily mean that it is surveillance testing. And so we just want to make sure that everybody is aware that if there's a facility or an entity is performing specifically COVID testing, because that's what this call is about, and they are returning a patient-specific result to a patient or a physician, that those facilities or entities need to be CLIA-certified.

I also just wanted to give you an update that we have put out new guidance. It was published on Friday and can be found on our website. And it concerns the reporting of SARS-CoV-2 results and the regulation that was put out earlier in the year that makes it a requirement for any CLIA-certified laboratory who is performing this testing to report to state or local health departments.

We've put out further guidance for our surveyors and what is to be looked for on inspection-- what they can be looking for. We've also added in that initially, it was if a CLIA surveyor came to a laboratory and found that that facility was not reporting results to state or local health departments that they would be an imposition or could be an imposition of civil money penalties. We are now going to be issuing a warning letter first. And upon revisit after the warning letter, if the laboratory is still not attempting to report those results to state or local health departments, that is when there can be an imposition of civil money penalties.

So what we put out on Friday-- there was a surveyor letter, there was surveyor guidance, and there was also a frequently asked question document, and all found together in one large document on our website. And I can actually put the link, so where you can find all of those documents and all that information, into the chat so that everybody can get it. And Jasmine, I'm happy to answer any questions if there are any.

JASMINE CHAITRAM: Thanks, Amy. I'm not showing any questions for you specifically. But I'll say the same thing, that if you hang on the line with us till the end of the call, I may come back and ask you a question.

AMY ZALE: Happy to.

JASMINE CHAITRAM: All right, great. So our last agenda item is our update from FDA-- that's the U.S. Food and Drug Administration-- is Tim Stenzel, who's also been on these calls before. Tim?

TIM STENZEL: Thank you. Yeah, hello again, everyone. So a number of updates and some questions from before the call that I want to address. There were two safety communications that we issued last week. One was on the tests from Curative, and the other one was on mutations. And I'll cover first the Curative safety communication.

So we recommend that you follow the labeling in the EUA summary and not use any off-label testing. They are authorized for symptomatic individuals only within the first 14 days of symptoms. The collection, whether it be nasal swab-- that these are self-collected collections of nasal swab or oral swab-- need to always be observed.

There is a risk, a heightened risk, of false results if these are not followed. The labeling is very specific and has very important reasons why we put on those labeling restrictions in their authorization. If anybody within the last 14 days has results that might be false negative, we do recommend that you test with another-- with a high-sensitivity molecular test to answer the question about whether or not they're infected.

Moving on to the mutations safety communication, as we all know, variants are increasing in prevalence. That is, a diversity of variants as well as some variants have become prevalent. In fact, one that I'll discuss, at least in the GISAID database, appears to be above 10% of all sequences. There are three tests that are mentioned in the safety communication.

Thankfully, at this time, we do not believe that there's any significant drop in sensitivity based on the variants. I'll go into a little bit more detail about that. We do want everyone to be aware of this potential for false negatives, as variants continue to persist and grow. That whenever there's an unusual negative result, that you consider testing with a different-- a test that tests for different parts of the virus. This is especially so for single-target assays-- those assays that only have one molecular amplification or detection method. Those that have two or more are more likely to not lose sensitivity due to variants.

One thing I want to make clear is that from the very beginning, for all authorizations, we have asked for in silico analysis of the developers, primers, and probes at least twice during the submission and authorization process, one early on and one near authorization, to make sure that their primers and probe sequences are inclusive of the vast majority of circulating SARS virus, at least as known in the databases that we have access to. The second is in about midsummer, because for all EUA-authorized molecular assays, we have all the primer and probe sequences, these are usually considered proprietary and aren't publicly known. But they're known by the FDA.

So we've created a database of all the primer and probe sequences. We also interrogate the GISAID and other databases on a regular basis, at least for the US sequences. And we look for any mutations that are popping up in relative frequency, and then search the database of known primers and probe sequences by developers. We then write letters to these developers and ask them to do an assessment while we in parallel do an assessment.

So as a result of those activities, which have now also covered the UK variant and the South African variant, we mentioned three assays last week. They are the Thermo Fisher TaqPath, the Linea, and the Mesa Biotech Accula. The Thermo Fisher TaqPath has three targets. One of them is the S gene, and there is an S gene drop-out due to the deletion 69/70 in the spike protein.

Likewise, the Linea assay is a two-target assay, and one of those is the S gene and drops out with the del 69/70. For both of the assays, we don't think that there's an overall drop in clinical sensitivity because they have a multi-target assay. Rather, they are useful perhaps for labs that use these tests to identify potential UK variants because the del 69/70 is not always associated with the UK variant.

In fact, in the US population at this point, we think that the UK variant is only a minor portion. We know for the Thermo Fisher assay that about 5% of Thermo Fisher positives had an S gene dropout, but nowhere near that have the UK variant. So determining whether something has the UK variant sequencing is required at this point. At some point, if the UK variant becomes very prevalent, then there may be a lot more of a one-to-one association with S gene dropout of the Thermo Fisher and Linea assays.

For those labs that are doing sequencing, we would ask when you can, to deposit your sequences. These databases are very important for the FDA to track variants in the population and their relative prevalence. So the relative prevalence is a lot more difficult to get at due to

the nature of how we enter sequences in-- how sequences are entered into the database. The more sequences that are there from everyone who is sequencing, the easier it is for us to track relative prevalence and for potential issues. And we'll continue our surveillance and update safety communications as required.

Moving on to the Mesa Biotech assay, there is a pre-base pair change, GGT to AAC, at the position of 28881 in the virus. And it does affect the TM and has a slight effect on the LOD. And all that information should be in the current package insert for the Mesa.

However, we do not believe that at this time there is a significant clinical sensitivity impact for the Mesa Biotech. It is a point-of-care waived test, molecular test. And so there's no reason to stop using this test at all. It's just important to be aware.

And all tests are subject to, of course, false negatives and false positives. And all tests are subject to variant imposition. So we're asking the community to be vigilant about this. And again, single-target assays are a little bit more problematic for this than multiple-target assays.

Moving on to the other prepared answers I have for questions, first question was, is the FDA currently working on EUAs for additional COVID-19 screening home antigen tests that will be affordable for all to do multiple tests per week without a device, with results within 15 minutes, and be available to all over the counter without a prescription and without symptoms? Of course, we've already authorized one home antigen test over the counter, and that's the Ellume. We anticipate that there will be more.

Of course, the FDA does not develop these tests. We rather receive applications and process them as fast as possible. Home testing, home collection, point of care, and very high throughput central lab tests are our current highest priorities and have been for a while.

And we don't determine what developers develop or what they validate for review by our team. We are open to any test that can add to the testing capacity and that are accurate. This does include direct-to-consumer and over-the-counter options that the home consumer can use, either in collections or in-home tests.

I think there will be a lot more home collections that will be direct-to-consumer and over-the-counter more quickly than there will be in-home tests. But as you know, there are some relatively inexpensive tests that have been-- well, one is the BinaxNOW™ has been authorized for home use, but by prescription. It does utilize a proctor or an observer, which does add to the cost. And we are encouraging developers to consider the OTC option for both home collection and home testing. We are not able at this time, due to the confidential nature of submissions, to talk about what are in-house and are currently under review.

The second question has to do with-- are changes anticipated to have LDTs to go back through the EUA process? At this time, we do not have any further information to provide. We are in

discussions still with HHS. And I think that, at least the questions that I got ahead of time, address things from the FDA perspective. Thank you.

JASMINE CHAITRAM: Thank you so much, Tim. I do have a couple of questions for you. The first one is, none of the SARS-CoV-2 serologic EUAs are approved with claims of determining immunization effectiveness. Could Dr. Stenzel weigh in on whether laboratories using serologic methods should use these methods to assess an adequate response to immunization? Or are more studies required to justify such a claim?

TIM STENZEL: Well, first of all, there's nothing in the labeling for these tests that would prevent clinicians and laboratories for assessing such questions. In order for us to authorize a test for such purposes, we would ask for data that we can review that would support such uses. So laboratorians and clinicians can use the test and apply it in the way that they see best fit.

But I would caution that I think that our understanding of all these things is still in the early stages. What is an adequate response to a vaccine? What does that mean? I've had questions around who should be vaccinated.

Should be we be testing people first with serology tests and only vaccinating those who are antibody-negative? So there's a lot of potential uses in which we're very open to exploring with developers. But again, we would want to see data. And finally, again, there's no prohibition for labs to use things-- authorized tests-- and clinicians to help make the best determinations for individual patients.

JASMINE CHAITRAM: OK, thanks, Tim. The next question is, my understanding is the Binax test is FDA-approved only for symptomatic individuals. Is this correct? Can you comment?

TIM STENZEL: No, it's not correct. It's authorized for those suspected of COVID. That could include people at risk. And then we have made very clear, including myself on previous calls, that except for the Curative test, which we've now had a safety comm, there are no authorized tests, diagnostic tests, that is-- molecular or antigen test-- where I have similar concerns, so other than the Curative.

Realize that if-- we have now 11 tests, one antigen and 10 molecular, that have been authorized for asymptomatic screening. Certainly encourage their use first and foremost if they're available to you. There will be a growing number because every OTC offering will require an asymptomatic claim. So anytime you see something that's OTC like the Ellume, they have gone through and achieved an asymptomatic screening claim for their test.

So again, all of the antigen tests-- I would encourage you to find it useful to use the direct antigen tests to screen asymptomatics. Understand the potential limitations. We don't have data. There was some data presented today. I would say it's great to have data. It's little bit hard for me to assess accurate comparative performance between a molecular test and an antigen test if we're not sampling the exact same body site. And that would be helpful.

Also, antigen tests-- their sensitivity falls off faster than with molecular tests following infection. And so understand that you could be three weeks out and detect an asymptomatic positive with a molecular test and be negative with antigen. And I don't know that there's anything wrong with that, right? I don't know that we need to be worried three weeks out on patients with a very low positive molecular test. Hope that's helpful.

JASMINE CHAITRAM: Thanks, Tim. You spoke to PCR tests and variants. Any concern with spike protein-based antigen tests not detecting variants?

TIM STENZEL: My understanding is that there's many variants that do affect both spike, of course, and the nucleocapsid gene, the N gene. And so the CDC has graciously agreed for the UK variant, which they're culturing, to test antigen tests. So we're in the process of reaching out to all the EUA-authorized antigen tests and asking them to send their tests and test kits to the CDC.

We'll provide instructions on how to do that. So the CDC's standing up that program now. We want to know how all the antigen tests do with regard to the UK variant. Obviously, if you don't have primer and probe sequences, it's a lot harder to assess the impact of a variant on either an antigen test or even a serology test.

JASMINE CHAITRAM: OK, thanks, Tim. This is the last question I'm going to ask you. Is the FDA going to gather a list of commercial tests which do and do not cover the variants?

TIM STENZEL: So we will be continuously scanning. And our current threshold is, other than the UK and the South African variant, which we don't think that there's any tests on the market-- that are EUA-authorized that are not able to detect those variants. We think everything that's on the market now can reliably detect those. If they have S gene dropout, it's then because they have multiple targets.

We have set the threshold for further investigation with developers at 5%. So when a mutation becomes prevalent to the point of 5%, then we generate a list of the potentially impacted tests. We send those letters to the companies, while we also independently assess the effect on the assay.

Now, you could have a single nucleotide variant that probably wouldn't affect even a single-gene test. And then also, you could have a three-base change. But if it's in the 5 prime end of a primer and overlapping, so it's only maybe two bases of the primer, and not three, well, it's likely to have an impact. But we do assess all of those. And as soon as we know or suspect that there could be an impact, we will make that information public. Thank you. I hope that addressed that question, too.

JASMINE CHAITRAM: OK, great. Thank you so much, Tim. Amy Zale from CMS, are you still on? Because I do have a couple of questions for you.

AMY ZALE: Yes, I'm here.

JASMINE CHAITRAM: OK, great. The first question is, if the certificate of waiver labs do not have recordkeeping requirements, how will surveyors be expected to verify that certificate of waiver labs are reporting all of their SARS-CoV-2 test results? And then it goes on to say, the EUAs do not indicate that there are recordkeeping requirements, only that they have a policy. And that QSL memo says that CMS is not prescriptive on the content of the policy regarding recordkeeping of test results, only that they have to have a policy reporting-- policy for reporting per the EUA.

AMY ZALE: That's right. And so under normal circumstances, there aren't record reporting regulations. But that's what our interim final rule with comment did, was to make it a requirement for Certificate of Waiver laboratories to do that reporting. And as such, there should be documentation that those test results were reported.

And so surveyors are going to be looking for whether or not those test results, positive and negative test results, were reported. And so under normal circumstances, under the normal regulations, there are not those requirements for Certificate of Waiver laboratories. But that is what the interim final rule with comment did for Certificate of Waiver laboratories, was to add that requirement.

JASMINE CHAITRAM: OK, great. And I've got two more quick ones for you, I think. The first one was about pop-up labs and if they should be reported to the state or--

AMY ZALE: To the state or to CMS, either one. But if you know that they're there, yes, I would report them so that we can investigate them.

JASMINE CHAITRAM: OK, great. And then the next one is, even if the entity being tested is an employee rather than a patient, such as for weekly testing, since the results are returned to the employer with the person's name, this is not surveillance, correct?

AMY ZALE: That's correct. It doesn't matter what the patient or individual or employee is actually called. If you are taking an individual's result and returning it to that individual or to their health care provider, it is not surveillance. It's diagnostic testing. And they need to be CLIA-certified to be doing that testing.

JASMINE CHAITRAM: All right, thanks so much, Amy. And we're right at the end of our call, so I'm not going to start another question. But I'm going to take this time to just remind everybody that our next call will be on January 25. And we hope that you will join us.

And that if you want to receive communications from the Division of Laboratory Systems, please send an email to LOCS@cdc.gov. And by doing that, you will also receive the announcements for these calls. I want to thank all of our speakers and presenters for joining us today.

I want to wish everybody a Happy New Year. I can't remember if I did that at the beginning of the call, but I do wish you all a Happy New Year. And thank you for joining us today.