Clinical Laboratory COVID-19 Response Call

February 8, 2021

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JASMINE CHAITRAM: Hello, everyone. I am Jasmine Chaitram. I'm the Associate Director for Laboratory Preparedness in the Division of Laboratory Systems. Thank you for joining us for the Clinical Laboratory COVID-19 Response Call. The Division of Laboratory Systems, or DLS, has been hosting these calls every other week since March 2020.

And our role has been-- previously before COVID-19, supporting clinical and public health laboratories and specific topic areas such as quality and safety, training and workforce development, informatics, biorepository, and data science. We've also been helping the laboratories with preparedness and emergency response. And in particular, response to COVID-19.

We serve as a liaison to the CDC Emergency Operations Center and we provide communication and coordination for clinical and public health laboratories. We've been having these calls, as I've mentioned. And those of you that have been tuning in for months now know the standard order of the calls.

I have showing here, our agenda. And I'm going to go through a couple of reminders and then we will get started. As usual, we have our important links as a reference. These slides do get posted to our preparedness portal, and along with our transcript and the audio from these calls. And so if you're referencing back to these slides, these are some important links that might be easy to get to and useful to any of you out there.

And here is our Preparedness Portal just in case you didn't know the address for that. Also, this portal contains our LOCS messages and archives of all the message we sent-- all the messages we sent through our Laboratory Outreach Communication System. And those are emails with important information on a variety of topics. Everything that I had just mentioned that DLS is responsible for, but these are COVID-19 specific emails.

The next call will be on Monday, February 22. These are calls that are happening every other week. They're from 3:00 to 4:00 PM. And we're glad that you can join us and hope you can join us for a future call. The training and workforce development group in our division is interested to know if you have any specific training needs, and we ask that you send us through LabTrainingNeeds@cdc.gov.

And then finally, when you're asking a question, please do that in the Q&A feature on the Zoom buttons in your call. We do not want you to submit those to the chat. Those are hard for us to track. We do try to answer all of the questions, either as many as we can during the call or some after the call by email. If you provide your email address, we can do that after the call if we don't get to your questions during the call.

We do get a lot of questions, and it is hard sometimes with the timing and all of the speakers that we have in our agenda to answer all of those questions. So the best way to make sure that your question gets answered is to provide an email. And if you're the media, please send your questions to media@cdc.gov. And if you're a patient, please direct your questions to your health care provider.

So I think with that, we are going to move into our very first topic, which is an update on CDC's virtual reality laboratory training course. And Joe Rothschild, who's also from the Division of Laboratory Systems, is going to give that update. Joe, are you on?

JOE ROTHSCHILD: Hello. So yeah, we have CDC's first-ever virtual reality training course. We launched it-- we launched a new update to it rather, today, that basically extends the learning objectives and gives it basically twice the amount of play time. It's around a 60-minute course now, all in virtual reality.

And in addition to our previous learning objectives, which were around setting up and working the BSC, we've added how to clean up spills, how to shut it down in an emergency situation, as well as how to decontaminate and deal with waste. So it's a great new training course. A really large update available on both the STEAM platform, and you could always get it through CDC TRAIN. If you'd like more information on it, head on over to cdc.gov/labtraining and you should see the icon for that course. And that's about it. Thank you.

JASMINE CHAITRAM: Thank you, Joe. Our next speaker and topic is going to be some information from a public health laboratory, the Michigan Department of Health and Human Services. And we have two speakers, Marty Soehnlen and Heather Blankenship. And they're

going to be talking about their efforts around sequencing. So thank you very much. And I guess Marty will go first.

MARTY SOEHNLEN: Thank you, everybody. We'll put our camera off back in just a second, but I'm Marty Soehnlen. I'm Director of Infectious Disease at the Michigan Department of Health and Human Services.

HEATHER BLANKENSHIP: I'm Heather Blankenship. I am a Bioinformatics and Sequencing section manager here.

MARTY SOEHNLEN: So what we are going to do is we're going to do a little bit of an overview of some of the sequencing that we have been doing for COVID here in Michigan, a little bit of an overview of what's going to happen. We have actually been doing sequencing since March of 2020. We identified our first case in Michigan the week of March 10th. Shortly thereafter, we onboarded sequencing.

We'll talk about some of the protocols and some of the expansions that we've done. For us, it was very important to do this as early as possible. We believe very strongly here in the surveillance aspect of things and being able to use whole genome sequencing for those surveillance activities, which means that everything that we've done has to be in partnership with our state epidemiologists. And with our local Health Departments, we are a home rule state.

And a little bit about our laboratory to give you a little bit of background, we have 165 staff members-- full-time staff members here at the laboratory. We cover newborn screening, chemistry and toxicology, virology, microbiology, and then various aspects of molecular and bioinformatics.

And we have specifically built up what we have been able to perform for whole genome sequencing over the last three to five years and are the Midwest training lead. So we assist other states in the Midwest region with being able to bringing on board various aspects of their own. So next slide, please. There you go, Heather.

HEATHER BLANKENSHIP: All right, so what is the purpose of pathogen genomics? Just to give a little bit of background. Next slide. So one of the big things that we do here at the Bureau of Labs already is investigation of outbreaks as part of our PulseNet groups. So whether it is PulseNet organisms or one of our viral organisms, Next slide.

Also, looking at transmission patterns. So how can we see either a virus or a bacterial pathogen go from one person to another? What does potential transmission dynamics look like? And how can we take a lot of these and overlay onto what we're doing for COVID? Next slide.

The next one is monitoring valence change, monitoring patterns that we see within the states. Most common one is going to be things like our antimicrobial resistance genes. But how can we

again look to see what different parts of the state we're seeing and how is Michigan comparing to the rest of the US? Next slide.

And lastly, how can we use this to help develop interventions, whether it's developing different public health actions that need to take place for a facility or a region, or whether it's helping to provide additional information to the scientific community to develop vaccinations, or identify potential areas that may cause a problem with our diagnostic tests in the case of COVID? Next slide.

So here in Michigan, when we started sequencing, we came up with five overarching goals that we wanted to be able to perform with the sequencing knowledge and still feed off of those pathogens genomics that we've been doing for other organisms. We've brought into five goals. So we want to identify baselines for the virus.

What do we see in different areas of the state? What do we see in Michigan versus the rest of the US? Is there something different? Can we look at examining transmission dynamics? Do we see how things are moving between different regions of Michigan, how things are moving across our international borders with our partners in Canada, or how are we seeing it move to other states that are neighboring ourselves?

Can we identify clinically important variants, whether these are variants that are going to impact diagnostic testing or these variants that may play a role in how we respond? Maybe it's something more transmissible like our B117 variants. Or maybe it's something that in the future, we see something that's going be associated with a different demographic group.

So can we identify these variants as they emerge? And can we contribute to the viral biology knowledge? Can we contribute data for vaccine development, and so forth? And lastly, can we examine cluster outbreaks? Can we look at a facility and help provide assistance to them? And if they have COVID outbreaks occurring, can we help them identify are there multiple introductions that may have occurred, or can we see that all within one facility, and what that may tell us?

MARTY SOEHNLEN: And for these five things, you'll find that one of the most important facets for us was getting this to a real-time status. And there was significant amount of work on the work flows, the way that we brought things in, how we prioritized certain specimens or needs within the laboratory to be able to do this as quickly as possible so that we can actually use this data for the epidemiology responses as we were going.

Heather will talk a little bit about some of the timelines that it takes on each of the steps. But essentially, we are doing this in a real-time status now, which basically means you're getting a result within a week's time whenever you have the sample in hand. Next slide, please.

HEATHER BLANKENSHIP: So our current status here in Michigan since March of 2020 is we have 3,400 published genomes, which means that these isolates were greater than 94% genome

coverage after sequencing, and they have now been published in the state. We have 2,900 additional sequenced genomes that are below that 3,400-- below that 94% threshold. However, all of these sequences are still screened. We're still looking to see can we identify variants. If we get enough of the genome that we can at least identify different mutations or potentially loop them into some of our cluster outbreak investigations.

And then lastly, we have an additional 1,780 samples that were screened, but we're determined not to have quality enough sample in order to pass it on the sequencing. And for that, we mean that when we're screening with the PCR, they have a Ct value less than 30 or 32. So anything above that, we will screen out and will not push through the sequencing.

MARTY SOEHNLEN: And in addition to the numbers that we've done here at our state public health laboratory, in summer of 2020, we were able to work with the University of Michigan's Medical Center and their school of Public Health. And they actually onboarded the sequencing themselves as well. They are part of the HIVE studies, which is one of the very large national influenza groups.

And therefore, they were very well situated to be able to feed data back into us. So they've also done an additional 1,500 approximate genomes that they published up. And there is a reason why we ended up being so stringent on this publish at the 94% coverage or greater.

And some of those-- where we are now, everybody asks, well, why not just upload everything and just dump it all in? And really there hasn't been a national consensus to this point on how to deal with that or what cutoffs different states or federal partners are using, or even academic partners.

So there are discussions that are starting amongst us within the states to say, Hey, I'm using this. What are you using and why? And that may end up fine tuning itself over time. But essentially, the 94% coverage is looking at a certain number of changes or areas that we may not be able to get a clean enough read-on to still make sure that we can very strongly tell what's happening within each of those genomes. Next slide, please.

HEATHER BLANKENSHIP: So this is a high overview of the three different facets of COVID sequencing. So we have our wet lab and actually put it on a sequencer. We have our bioinformatics and analytics afterwards, and then how to communicate and what we're going to do with this information so it's actually useful, not just sitting in a database or sitting on hard drives. And so regardless, each one highlights the differences among those. Next slide.

So within sequencing, we do a total nucleic acid extraction. That nucleic acid is then turned into cDNA before we do a target amplification with PCR in order to greatly increase our chances of sequencing SARS-CoV-2. That information is then gone through library prep and put onto a sequencer. So a little bit more in depth of each of these steps of what we are performing and how we're performing them. Next slide.

So for nucleic acid extractions, we're running a wide range of extraction platforms. So far, we've not seen a difference among any of these extraction methods in the sequencing afterwards. A number of these extraction platforms are ones that we are also using for our COVID diagnostic testing in-house. Next slide.

So what do we sequence? As we mentioned, it's going to be anything with a Ct of less than 30 to 32 based off of our PCR screen. So this can either be with the CDC primer panel or with the Thermo Fisher, depending on how many samples and what platform it got on that day.

Epidemiological interest. So if it's within a reasonable Ct value. So if we have a sample that is a 31, 32, potentially up to a 33, it is one that we will put through. And we will just make sure we run it in duplicate or triplicate for all of the process of doing a PCR amplification and then putting on the sequencer, just to ensure that we have the highest volume of that sample that we can to potentially pull the rest of the genome.

And we're also trying to get representative sample distribution from different clinical sites around the state and having them send samples in for surveillance so that we do not lapse in having a geographic or demographic area of the state that we are missing.

MARTY SOEHNLEN: And here in Michigan, we have eight emergency preparedness regions. And it is very, very different based on where you're at in the state with us having two peninsulas. The Southeast Michigan area is the most populous. That's going to be the Detroit metro area – it also has the largest number of universities and so forth.

However, we do find that things can travel and be more vacation oriented and hunting oriented areas of the state, which are going to be along the lake shore regions and then within our upper peninsula.

HEATHER BLANKENSHIP: Next slide. So different sequencing prep. So right now, we are running the ARTIC V3 primers using both Nextera XT and Nextera Flex and putting it onto both NextSeq and MiSeq. We're in the process of switching over to using the QIAGEN QIAseq, which will then also go through our Nextera Flex or Nextera XT, to go on to our MiSeq and NextSeq respectively. Anything running our Nextera XT and going on for NextSeq is also being done with our Tecan automated platform, which is one of the reasons why we chose to stick with our Nextera XT for that platform, just because it was already coded into our Tecan, and was easy to print on that way.

MARTY SOEHNLEN: And as far as instrument numbers go within house, here in Michigan, we have two NextSeq 500 instruments, and we have four MiSeq instruments, and then we have a pair of Oxford Nanopore instruments. Next slide.

HEATHER BLANKENSHIP: Alright, so going into our bioinformatics of what happens once it comes off of any of those instruments, and what the pipelines look like, next slide. So, pipelines, it's going to really depend on the state and the location, and the resources that are available,

whether it's going to be Command-line or packages. Some packages that are currently available in CLC Workbench, by Numerics, Genius, or running something that's in Command-line. So, here in Michigan, we are running our own Command-line package and pipeline that we have developed internally. We've been looking at QC of the data in our pipelines to try and decide what thresholds are we going to use for making our data public, or even utilizing for analysis. We're using a 50 X3 coverage for the isolates as well as a 94% coverage, in order to determine that it's high quality data. Next slide.

So different public repositories. So GISAID is going to be our consensus sequences. For NCBI, it's going to be our raw sequencing data and our consensus sequences. The one difference and caveat with NCBI is requiring that a confirmation of all human reads are cleaned from the data before it is pushed to NCBI. That's why there's going to be a little bit of a lag between GISAID and NCBI, just because there's this additional confirmation step that has to occur. Next slide.

So, lastly, once we have the data, how can we communicate, how can we utilize this data so it's actually being put forth to public health action? Next slide. So how can we use data for public health action? Next slide. So, we can overlay the epidemiological and genomic data. I like this figure just to show how many different ways we can take different demographic data, geographic data, a lot of our epi metadata, and overlay it onto our genomic sequences and phylogenetic trees in order to give us an indication of what's occurring within the virus in the populations. Next slide.

So, how do we do that here in Michigan? In Michigan, we develop our own internal nextstrain build. We have an interactive visualization, which has all the metadata and gets sent to our state epidemiologists. But we also have a PDF version of this report that looks something like this, from one of our older reports back in September. Next slide.

So, each of our reports will have a summary page. It's going to tell us epidemiologists what's occurred, what is new, what's changed, some of the page numbers of key information that they should be turning to, that's new in this report. And it's going to give the new update of how many genomes we have sequenced at that time. Next slide.

We'll then have our sequencing purpose. So these were the ones that were mentioned earlier in the presentation. Just so that they have an idea of what's going on and why we are sequencing here in Michigan, in case this report is given to an epidemiologist that has never seen COVID sequencing before, and wants to understand the background of why this is occurring. Next slide.

We'll then do a basic SARS-CoV-2 overview, just in case, again, this is someone that has not been fully involved in COVID at this point. That way, they have an idea of some of the basics of SARS-CoV-2, or they have a landing point that they can go back to of some of the basic information of SARS-CoV-2. What it all means. And they can point to this as a resource. Next slide.

We'll then have a big overview of aggregated demographics. And then from here, we'll actually go into-- I'm not including it here, since it is internal data. But we'll go further into outbreak investigations, down to our county level, and look at how specific facilities are being pulled out and presented. Next slide. We'll also overlay a bunch of metadata. One of these is the status of whether they are deceased or alive based on the sampling data that we have. We have additional ones that we can overlay, such as gender, or--

MARTY SOEHNLEN: Race and ethnicity, location of whether they are urban or rural, things like that.

HEATHER BLANKENSHIP: Next slide.

MARTY SOEHNLEN: And some of the things that end up happening with those forms and the information that Heather was just talking about is, not only has it been important for us to train our state epidemiologists on how to understand and how to pull the data from mixed strain so that they can do it live any time that they need to as we upload things, but also to work with our local health departments. So we've done several recorded and live webinars for them, where we actually talk to health officers and the medical directors through what we're seeing, and how they can look at things at a certain county or regional perspective, and what that may mean as they try to track things from a specific facility. If they've had multiple point introductions, or a single point introduction, how can they make decisions on if they need to change some of the practices for what quarantines or behavioral changes are happening within their area.

We also work with our healthcare providers. So, as an overarching thing, we provide an overview, we have weekly phone calls with all of the lab directors of clinical and commercial labs, we give them an idea of types of things that they have seen or had available. We will actually be doing our second major webinar presentation for them in the next week, and those types of things are very similar from the fact that, although we bring it up a level so that we don't have county data or anything that would be traceable back to specific people for the lab directors, at least they're understanding what's happening. And if they need to make decision processes and see data associated with their facility, compared to the state as a whole, we can help them do that.

And then one of the biggest things is, in the Midwest region, we are partnered with the state of Wisconsin. This works incredibly well for our advanced molecular detection work, and the Wisconsin laboratory is the bioinformatics regional resource that is headed up by Kelsey Florek. And then on our side, we handle the training laboratory aspects, which is headed up by Heather Blankenship here. And together, they end up teaming up to be able to train, and develop code, and do things for other states. That has been extremely successful, especially during COVID. Kentucky, Ohio, have now been brought on board, Indiana is in its next stages, and Illinois is in the very starter processes, which will complete our region with everybody being at the same level and being able to do the same types of capabilities. Some of them will just do the packaged product, like what Heather had mentioned, that there are different ones available.

Others may choose to go more full bore, like we do, where you may code it yourself. But there are options, and that type of training is occurring.

And otherwise, I think we are happy to take questions, or wait until-- we end dependent upon whatever Jasmine would like us to do.

JASMINE CHAITRAM: Thank you. We did get a number of questions. I'm going to ask you two of them while we're on the call. Just because of time, I'm going to limit it to two, but I will encourage you, if you want to, to look in the Q&A box and feel free to respond to the questions that are there, that are relevant to your presentation. The first question says, could you kindly comment on additional consent required to do this testing, the sequencing? Is it bundled into the original test?

MARTY SOEHNLEN: So, for us it is, but the data is not returned in any way back to a patient or provider. So it's truly from a public health surveillance standpoint. We keep all of that data internal to us. We may provide a regional perspective, meaning one of the eight preparedness regions, but you would not be able to break it down further than that unless you happen to be one of the state laboratory or state epidemiologists assigned to this data. We are in the process of working to do a full laboratory developed test, or an LDT. We are a CAP laboratory here, so we would have to follow that process. It is not as easy as some of the other types of tests, so it is a very, very strenuous process to get to that point.

There are a lot of reasons, in my personal opinion, why you may not want to return this type of data back to a patient or clinician, because it's not really designed for treatment, or that type of thing rather being more useful from the public health standpoint of determining what's happening for quarantine and so forth. And I realize there may be many other opinions or views on that throughout the country. But that's the way that we do this here.

JASMINE CHAITRAM: OK, thank you. The next question is, do you focus in on PCR results that are positive for two gene fragments, but negative for the S gene, which may be due to the presence of a more resistant variant?

MARTY SOEHNLEN: Ah yes, the S drop out. So, we do not specifically, although we will happily take all S dropouts. Here, if it comes through our Bureau of Laboratories, meaning our state public health laboratory, it automatically reflexes, if it meets criteria, to go to sequencing regardless. Otherwise, we ask all of our clinical and commercial partners in the state to send us as many as they can, or at least a set number on a weekly basis. And then we may reach out and say, hey, do you have anything that's an unusual age group, or did you get any bizarre clinical presentation, or do you have something from this county, because we're not seeing much of that. Can you help ramp those numbers up for us?

So, by having all of us involved and being able to have those sent to us, Michigan public health code has allowed that to happen, so that they can pass it on to us as a public health authority. And then we just go ahead and do the work necessary behind the scenes. But again, we do not

return something directly back to them. But if we were to find a variant of concern, or something in there that raises eyebrows, then we talk to the state epidemiologists, who will make the appropriate decisions with the local health departments, and who may or may not choose to speak to the facility directly. That's all handled by them.

JASMINE CHAITRAM: Great, thank you for the answer. And as I mentioned, there are still several questions in the Q&A box. Feel free, if you want to go in there and look at them, and type an answer, and all of our participants can see your responses. And that would help us on saving some time. If you want to just take a second and thank you, and Heather, Marty, both of you, for being on the call today. Really appreciate the time you've taken to speak with us.

So, I'm going to move on to our next speaker, who is Vivien Dugan. She was on the call last week, and is going to give us an update, since this is a hot topic, lots going on with the variants. And Vivien, I do have the link to the interactive map, and I'm going to pull that up now. And hopefully everything will go smoothly. I don't normally do this, but here we go.

VIVIEN DUGAN: Excellent. Thank you very much, Jasmine. That looks great. Well, thanks for having me today. It's good to be with you all. And that's a hard act to follow after that talk, so Heather and Marty, that was a really nice summary of all that you're doing in the sequencing and genomics space. I'm just going to cover, very briefly, where we are with variants. And so most of you are probably familiar with CDC's variant map. That's updated every Tuesday, and Thursday, and Sunday, by 7:00 PM. And this is based-- you have to excuse my friend here. This is based on data that is generated either by CDC from specimens collected and then sent in through our National SARS-CoV-2 Surveillance Program efforts, or data generated by public health labs across the US. We also have CDC contract labs that are sequencing its Illumina, Helix, LabCorp, and Quest Diagnostics, that are getting specimens in for diagnostics, running the diagnostics, and also sequencing.

So based on what we have today for B117 variants, this is the, again the variant that was first detected in the United Kingdom, we have 690 reported cases in the US, with 33 states reporting. For the B1351 variant, that is the variant that was first detected in South Africa, the reported cases so far are six, and we've got three jurisdictions reporting. And then for that P1 variant, this is the variant that was originally detected in travelers from Brazil and Japan, but now also in Brazil and other parts of the world, there are three reported cases in the US with two states or jurisdictions reporting. If you scroll down a little bit, you can actually see we try to keep enhancing this map, and so right there, see for the number of cases there's a little key. You can see there's filters. So we've added these filters, it's right under the numbers in that box of number of cases. And right now it's showing the variant B117. But you can actually select from that filters menu down to pick the ones that you want to see. The P1, the B351, to try and make it a little bit easier to show which jurisdictions have confirmed a variant at this time. Again, we are updating the data Tuesdays, Thursdays, and Sundays by 7:00 PM.

Kind of a little bit related to the variant detection, we are requesting specimens under NS3 through a process we're calling enhanced surveillance. So our NS3, National Strain Surveillance

for the US, is-- the guidance is on the APHL public health website. It's also on our website, on our genomic surveillance landing page. So you can access it there.

We recently updated this guidance in that enhanced surveillance section, and this is where we request specimens representing areas of interest. So this is where we will request certain numbers, or up to 20 specimens per jurisdiction, for B117 variants, B135, the P1s. We've also added vaccine breakthroughs as another area, or specimens that can be submitted through NS3, on a weekly basis. And then we've added the P1s most recently, on Friday. And another note to kind of keep aware of that from CDC'S perspective on the national level, we actually have an enormous number of B117 specimens. And so this is because, as these specimens are coming into CDC, we are analyzing the genomic data based on the sequence, and then we are shuttling some of those, a subset of those specimens, into the labs for attempting to propagate the virus, and then ideally to characterize these viruses in the lab, through a bunch of different in vitro, as well as in vivo, assays. So that is our kind of area that is changing.

So this is where we will post and update the NS3 guidance, to reflect the topics or the particular variants or certain types of specimens that can be included and sent to CDC based on what's happening. So, most recently the B117 variants, because we have so many, you can still report them in, and public health labs have been doing a great job with that, where we still want to know if you're detecting B117 variants in your jurisdiction. And so you can still send that data into our functional mailbox. But as far as sending specimens in for sequencing, at this point we're not taking any more, just because we have sufficient numbers to propagate in the lab. So we're working through those to get a good number of those specimens actually grown for viruses. Again, also another reminder is that the viruses that we do isolate, propagate at CDC are put into BEI, which is a national resource funded by NIH to make these regions and resources available to labs that are interested, or qualify of course, with working with them at the higher biosafety containment level if needed.

The other change I can just kind of briefly talk about, with our surveillance in general. As we are trying to get up to our target number of 750 specimens from public health labs on a weekly basis. Last week and this week were the first two weeks that we started to really receive those specimens in, and we're getting quite a number, which is fantastic, and we're very thankful for all the contributions that the jurisdictions have been making. One thing we updated in that guidance, that again was updated on Friday, besides the enhanced surveillance and the different types of variants that we're looking for. We have the option for public health labs to ship samples weekly for half the number that we have in our guidance, or you can continue to ship on a bi-weekly basis.

One thing that's very important, that we've worked with some of our modelers in-house to work on, has been, how do we increase the ability to detect variants? And in some of the modeling studies that have been done, in-house again, they're still being refined, but an important thing to note is time. And so this lab time, which is the time that it takes from specimen collection to the actual sequence, that time really matters for variant detection. And so we've adjusted our National Strain Surveillance guidance to request that specimens were

obtained within seven days of the collection. So we're requesting more recently collected specimens, again, for drilling down and getting a better picture of what's currently circulating.

And so that's kind of a big level overview of some of the variants and the National Strain Surveillance activities. But, happy to take questions, at the end or now or whenever folks, or whenever Jasmine, is ready for that.

JASMINE CHAITRAM: Hey Vivien, thanks so much. You answered this question that's in the Q&A, but I'm going to ask it again, because I think it's one that's important, probably, lots of people are wondering, and maybe they didn't hear you say it. But the question is, is there a good resource for obtaining confirmed positives of the variants for validation purposes?

VIVIEN DUGAN: A good resource to confirm. Yeah. I mean, sequence-- it depends on the variant. The S-gene target failure, which I think Marty and Heather mentioned, that was a luck of the draw type of a way that we were able to start finding and drilling down to find these B117 variants. Is it a perfect proxy? Not yet. But for the other variants, like the B1351 and the P1, sequencing is really the only way, right now, that we are aware of to really confirm what they are. And I know that's often challenging for many states and jurisdictions that are not sequencing a large number of specimens, or really any specimens, and they're relying on CDC to send their specimens in through NS3.

Certainly we expect that we will get variants a couple of different ways, coming in to CDC. And so we can offer to sequence for you, if you submit them in through your NS3 specimens, or through your targeted surveillance. Another thing that can be done, there are, it seems to be research use only assays that are becoming more and more publicly available. They're preprint status, mostly online. And so there seems to be a good amount of interest and effort in these research use only methods. Either real time PCR, or, I think there's a couple of other different ones out there.

And we're trying to amass all of these different preprints as they're coming out, so can be able to make it available as a resource for if certain labs are interested to try and narrow down, either prioritize their own sequencing efforts internally, or to prioritize, maybe, what they're sending in to CDC. And so, those are kind of out there, and they exist. That's one option to think about. Not necessarily confirmation, because it's research use only, but it's an option.

But short of sequencing, that's where we are right now. There may be efforts, maybe later on or to go down the diagnostic route for particular variants, but at this point, those UA-cleared assays are not available.

JASMINE CHAITRAM: Thanks, Vivien. Really appreciate you joining us. I know this is a super busy time for you, so, really appreciate the time. We're going to move to our next speaker. And our next topic and speaker is going to be about vaccine breakthrough case investigations, and Leisha Nolen, from the CDC COVID response vaccine breakthrough team, has joined us today. Leisha?

LEISHA NOLEN: Hi, this is Leisha Nolen. And I'm going to apologize. I'm not going to turn on my video, because I know that causes my connection to die. So, voice only today. Yeah, I think this really leads on very nicely from what the other two talks have been, and that this is sort of the opposite direction to look at variants. So I'm part of a team here at CDC specifically looking at vaccine breakthrough cases. Next slide. Are you doing slides, or am I? You're doing slides right?

JASMINE CHAITRAM: I'm doing slides.

LEISHA NOLEN: Okay. And so where you're specifically interested in looking at those people who have been fully vaccinated against SARS-CoV-2, yet still get COVID infection. And so what we're really looking at is to see if there's any trends or clusters, and what is causing this. And so we're looking both for characteristics of the patients who get these vaccine breakthroughs, characteristics of how the vaccine was handled in terms of cold chain and administration, but then of course, looking at characteristics of the virus that causes these breakthroughs. Next slide.

So, the definition that we're using is that we're calling it a vaccine breakthrough. When an infection occurs within someone who has been fully vaccinated against SARS-CoV-2, and it's 14 days after completion of that full vaccine series. And we consider both SARS-CoV-2 RNA or antigen positivity to represent a breakthrough case. And then one thing we are doing is an exclusion, is, we're keeping out people who have tested positive recently in terms of trying to eliminate the possibility that we are detecting people who are long term shedders. Next slide.

So, the way we have the investigations laid out is that we are asking all cases to be reported to the state health departments. And we're giving them access, so that they can do direct data entry at the state health department level. And the information we're collecting is a lot of epidemiologic data, such as demographics, health risk factors, vaccine details, and the details about the COVID infection. But then we have the laboratory characteristics which I really am here today to talk to you about. So, one, you're just aware that we're doing this, and that you aren't surprised if you're ever reached out. So, we are doing two different things. We're both looking at viral characterization, and then rarely, we are also going to try to look at immune characterizations. Next slide.

So, viral characterization, as I assume we all could have guessed, we are interested in seeing what the genomics of the virus is that causes these breakthrough cases. So, in the case that some sequence is already available from that specific case that was done at a local lab, we are happy to accept that whole gene, or those genomic sequencing. But if it hasn't been done locally, CDC is taking samples so that we can do sequencing ourselves. So we are able to take viral isolates, RNA or respiratory samples, and do evaluation on those. If we are able to get a viable virus, we're also interested in looking at viral neutralization assays, to see if the virus that caused these breakthrough cases are able to avoid antibodies that are elicited in normal vaccine patients. So, that would require viable samples, which we know is not always collected and maintained in that way, but-- So these are-- genomic sequencing is really the main goal, with a possibility of doing neutralization assays with a second goal. Next slide.

So as I mentioned, we're willing to use different types of respiratory samples. We are ideally using the original test samples, the one that the person was collected that diagnosed them with COVID, and so in which case we'd try to find to see-- we'd usually contact the laboratory to see if they possibly have any of that sample left. And I know different laboratories have different time periods for how long they hold samples. And we understand that, and we understand it's hard to hold samples for very long. But you might be contacted, as a laboratory, to see if you still have a sample that tested positive on a breakthrough case patient.

And just as simple details, we do ask that these samples be put in screwtop tubes so that they can be shipped without losing material. And we also will provide you with a specific sample ID to include on it. And then we'd ask to hold it at negative 70, or really as low a temperature as you can. It doesn't have to be negative 70 until we can get it to shipment. And then CDC would give you the specific paperwork for shipment. Next slide.

And I mentioned a minute ago, we are interested in doing immune characterization. We certainly want to see if breakthrough cases occur in specific people who have decreased immune response to the vaccine. However, this becomes quite complex, because as you know, people are going to have the immune response to the vaccine, but if they recently had an acute infection, they're also going to start to have an immune response to that acute infection. So it's really hard to distinguish the two. So therefore, we actually are only doing this more passively in terms of if there is existing serum that was drawn for other reasons. We would ask to get any residual for that, from these people, if it was taken sometime between the end of their vaccine series and before seven days post infection. And we understand and expect we'll rarely have access to these samples. This is just something that, if we have the opportunity, it would be very interesting to see if people have evidence of immune response and still get still get breakthrough infection. But this is going to be a rare occurrence. Next slide.

So, what are the roles we feel that the clinical lab can do? So, one thing is identifying samples that are from breakthrough cases. And I think a lot of times, it's going to be the health departments reaching out to and indicating that there is a breakthrough case that was tested at your facility. But I do know some sites are adding a vaccine question to their requisition forms, so that they can quickly tag which samples are from people who are fully vaccinated. And that way, they sort of put those as a priority to hold a little bit longer if possible, if they do in fact, test positive. And I think that is something, really, depending on the laboratory capacity and abilities, something to consider.

And so, if possible, if those samples are identified, we'd ask to have any positive sample from a breakthrough case be held. And then we can work with you to transfer samples to the CDC for testing, or for viral sequencing if it's already not being done in your local place. And as was just mentioned, the forms we're using are very similar to NS3, but we do have a specific code for this project. So they do not go into that specific flow, but get sequenced specifically for this evaluation. Next slide.

And so with that, I can just end, ask and answer any questions. Here is our functional email box. It's specifically for the vaccine breakthrough case investigation team in case you need to reach out to us. So, thank you.

JASMINE CHAITRAM: Thank you so much, Leisha. We don't have a lot of time, and I'm going to try to squeeze in a couple of questions. First one is, are you looking at severity of symptoms, for partial protection, let's say?

LEISHA NOLEN: Yeah, so, this analysis is really-- we're doing a very basic analysis of that. We're just looking to see whether or not the person needed to get medical care, needed to be hospitalized, needed ICU care, or passed away due to the infection. So we're getting very, very rough data about that. We are hoping to do more focused special studies where we can do targeted sites, where they will get more extensive information. This is intended to be a nationwide surveillance system, and therefore, to burden the states with more data collection just did not seem feasible. So in this large level system, we are not getting very detailed information.

JASMINE CHAITRAM: OK. And, probably not, but do you have any sense of the relative percentage of breakthrough cases versus all vaccinated individuals?

LEISHA NOLEN: So, I guess I'll just, I'm not sure exactly the question, but-- So, we do know this vaccine is 94% to 95% effective, the two that are currently in the United States, approved, authorized. So we do expect that there will be a number of breakthroughs. When we did a calculation, very, very rough calculation, we're estimating there should be around 100 a day, right now. But of course, those numbers are going to change as more and more people get vaccinated.

JASMINE CHAITRAM: OK, thank you so much. As I said to some of the other speakers, there are a number of questions still in the Q&A box. So if you are able to go in there and answer some questions live, that way everyone can kind of see the responses to them. Because I think there's a lot of interest in this topic as well. But I just want to thank you, again, for joining us this afternoon. And we are going to move to our final topic. Our FDA update. Which usually is given by Tim Stenzel from the US Food and Drug Administration. And Tim, we're ready for you when you are.

TIM STENZEL: All right, thank you, Jasmine. Hello, everyone. We had just one question submitted beforehand that I wanted to go over. And then if there's time, I can take any additional questions, now or later. So, the question was, if self-collect swab was not part of the premarket data submitted for the FDA EUA, Emergency Use Authorization, then does the use of self-collect swab with an assay having an FDA EUA make the test an LDT, or Laboratory Developed Test? If self-collection occurs within a healthcare facility, the FDA has stated in our frequently asked questions on our website that on-site collection, self-collection, is appropriate for a midturbinate and anterior nares swab collection. And a submission is not required, but

this provision is, unless specifically prohibited by the EUA testing labeling, which, to my knowledge, I'm not aware of that being prohibited.

Nasopharyngeal and oropharyngeal specimens are not appropriate for self-collection. And while the FDA does not require a submission for this modification in a healthcare facility, self-collection, if it is not in the EUA authorization, it would be considered off-label. If the question pertains to home self-collection, it didn't really clarify in that point, the FDA does require an EUA authorization for home collection before initiating any home collection testing. And so that hopefully addresses that question. Back over to you, Jas.

JASMINE CHAITRAM: OK, Tim. Let me see if we have any other updates for you. Not updates sorry, questions for you. So we do have one. It says, can Tim recap the vendor kits available as over-the-counter now?

TIM STENZEL: So, on the FDA website, for the authorized tests, you couldn't put in a search function for home, and home collection, home test. There is one home test, the Ellume, that is currently over the counter, and there are two home tests that are by prescription. And then there are, I think, now over 40 home self-collection kits. And a number of them are now over the counter. I just don't remember which ones they are. But if you go to the FDA's website, you can search on over the counter for molecular, and it'll bring up all those opportunities and all the labeling, which explains the testing that they did for validation, and the performance.

JASMINE CHAITRAM: Great. Thanks, Tim. I don't see any other questions for you at this time. Well, OK. First of all, let me just make a comment. There is a question that's about CMS updates that was on the agenda. And initially it was on the agenda on Friday, but we had to remove it. CMS is unable to give an update at this time. Hopefully they will be on the next call. And then the next question, Tim, I'm not sure if you have information about this. It says, do you know when we will have more information on the allocation of Ellume to the states? You probably don't have that information, as I think that's a HHS-managed task at this point in time. And we can have--

TIM STENZEL: That's correct. That's correct. They're managing that, not the FDA.

JASMINE CHAITRAM: OK. So we'll have somebody from CDC respond to that with more information after the call. I think that's it for questions for today. And so we have managed to able to finish on time, or even just a minute or two early, which sometimes doesn't happen for us. So, with that, and just a couple of reminders, then, that our next call is on February 22 at 3 o'clock. And if you're not receiving emails, please notify us through LOCS@cdc.gov, that's LOCS@cdc.gov. And we can put you on our distribution list, and that will also give you announcements for all of these calls. And, just wanted to thank you all again for being here, for all the hard work that everybody is doing out there. We know that it's been a tough, more than a year. Tough several months. So, thank you for joining us, and stay safe.