Welcome to the "Changing TB Isolation Practices New Guidelines for Molecular Testing" webinar. I'm Kelly Musoke, the Director of Education at the Curry International Tuberculosis Center. We have at least 700 participants joining us from across the United States, and we know some of you are viewing in groups. This is a collaborative training between the National TB Controllers Association, the Association of Public Health Laboratories, the Southeastern National Tuberculosis Center, and the Curry International Tuberculosis Center.

We'd like to provide the websites for all the partner organizations in case you wish to learn more about any of us. This webinar has been produced by two of the RTMCCs. We always like to ensure that everyone knows while our in-person trainings and clinical consultation are divided by region, all of the RTMCC products and webinars are available to a national audience. Since this training has many new participants listening in today, I'd like to highlight that each RTMCC provides free clinical and programmatic consultations to U.S.-based clinicians. The responses are generally provided within one to two business days.

We'd like to thank all of today's presenters, as well as all the members of the planning committee. All of today's faculty members have signed a declaration of disclosure and have indicated they have nothing to disclose. These are the learning objectives for this webinar, outlining the key points that we hope to touch on. But now let's move straight into our session today.

It's my pleasure to introduce today's facilitator, Dave Ashkin. Dr. David Ashkin is the Medical Director and Co-Principal Investigator for the Southeastern National Tuberculosis Center. As the current medical director of the Florida Department of Health's TB program, Dr. Ashkin is responsible for the medical management of all of Florida's TB patients, including those most complex cases which are hospitalized at the state's two contracted TB units.

Dr. Ashkin is a board certified pulmonologist and intensivist who trained at St. Luke's Roosevelt Hospital in New York during their outbreak of MDR tuberculosis. He also did his pulmonary fellowship at the University of Miami during their outbreak. He has published extensively on the care and treatment of TB. Dr. Ashkin also serves on Florida and national advisory panels for controlling TB and was recently instrumental in restructuring the Florida TB programs to better address TB elimination in the state. Dr. Ashkin.

Hey. Thank you very much. Really appreciate it. It's such an honor to be here today. We're really excited about this. I have to say that, you know, it's always, you know, strange for me. I mean, one of the things I really love about tuberculosis is the history. And, you know, for many of us in the field, you know, the nice part about TB is most of the treatments we do, most of the diagnostics we utilize, and most of the procedures we follow have been in place for decades and decades. But as you know, it's been a really exciting time right now for TB, at least in the United States. We're seeing, up until this year, you know, a dramatic decline in the number of cases. And with that we've also seen new technologies and even some new meds, something we never thought we were going to see. And with that, you know, it's been very, very exciting.

But, you know -- it has posed the TB community a challenge that with the declining cases, with new technologies, the question is how do we incorporate them. And with that, we are here today to talk about the new technologies and some new consensus guidelines in order to talk about maybe how we can take people off of isolation quicker or, better yet, detect those with tuberculosis faster. And we have a distinguished faculty today to discuss that. We have John Bernardo, Dave Warshauer, and Neha Shah. And we're going to discuss different aspects of these new consensus statements.

So, without further ado, can I see my first slide? So I stated before that all of us, you know, in tuberculosis have always been impressed with the history. And for many of us who have been in tuberculosis, I don't think we could have ever had a lecture that didn't include this slide here. For many of you, this is an early 1990's CDC slide that talked about the number of cases of nosocomial HIV multidrug-resistant TB outbreaks. And as Kelly was stating before, I trained at this hospital right here in New York City. This is while I was an intern and resident during the years 1986 to 1990 where we saw the nosocomial outbreak.

And, you know, unfortunately or fortunately, I moved to University of Florida -- I'm sorry, University of Miami to do my fellowship. And we had an outbreak there. And I think we'd agree that these really, really influence many of us in TB on how -- what we have to do, not only in the process of diagnosing TB but what happened when TB patients were in facilities, congregate settings in order to diagnose them.

And as you know, these outbreaks not only affected the patients but also affected the staff. And if you look in many of these outbreaks, anywhere from 20% of 50% of the staff that took care of these patients converted. And that's significantly -- not only did these staff members convert, but many of them actually developed active TB. And as you can see -- and this is an old study -- nine of 19 of the health care workers who developed multidrug-resistant TB actually died of it, and many of them were immunosuppressed. You can see that the median age was 37 years old. So this process of having patients with tuberculosis in hospitals in congregate settings was significant.

You know, I know many of you on this call have heard over and over again what contributes to these outbreaks. And obviously it was a time when we had many, many immunosuppressed individuals in units that were housing HIV-positive individuals. Obviously, at that time, we also weren't recognizing TB, I mean, we weren't thinking TB and we weren't diagnosing it, and we definitely didn't diagnose multidrug-resistant TB. But one of the biggest issues was we were not recognizing, we weren't isolating these patients. And even when we isolated these patients, we were not keeping them in isolation long enough if they, in fact, had TB.

And because of these occurrences, the CDC, in 1990, came out with a document, "The Control of TB in the United States," which included recommendations for how to isolate patients with tuberculosis, or at least suspected of TB, and other precautions. And since then, as you know, they came out in 1994 with the guidelines, and again in 2005 to update them. As you know, these original guidelines really looked at not only just, you know, all aspects of isolation and airborne isolation and infection control when it came to TB in hospitals. And as many of you know, it really recommended the use of administrative, meaning what policies had to be in place in order to isolate and how long should somebody be isolated. Also, what kind of respiratory protection should individuals wear as well as what kind of ventilation or engineering procedures needed to be followed.

And as you're aware, I mean, this is, like, one of the gold standards. You know, you can't be in TB without -- especially if you work in a hospital where there's the famous rule-out TB protocol, which always traditionally included the three sputum smears. And originally, as you know, it was three sputum smears collected early morning. And it was always recommended that you use three negative smears to remove somebody from isolation. But I want to emphasize something that's really important, realize that these recommendations were not based on studies, I mean, no one ever looked at is two sputums okay, originally, or three.

It was really based on historical data that looked at, you know, first of all, what we knew about transmission of TB. We knew that if you look at patients who were in contact to somebody who had a positive smear, about 30% to 50% of those contacts became infected. As well as we also knew that smears, which were relatively rapid to get the diagnosis, had about a 50% to 60% sensitivity to diagnosis. So when they came up with these guidelines, the idea was based on, well, if we do three sputums, one every day, we had a pretty good chance of knowing who might be -- have active TB.

You know, but I think one of the things that always happens, and I wanted to stop and kind of begin to talk about, was that, you know, I think many of us forget that active tuberculosis disease does not necessarily equal infectiousness. As a matter of fact, there are patients who have tuberculosis that are not contagious. They don't spread TB. And, matter of fact, studies going back early on, I mean, back to the 1960's, studies showed that only about 20% to 50% of patients with TB are thought to be able to transmit disease. More than half actually, even though they have active disease, do not transmit disease. I don't want to take anything away because those that do -- that are contagious, they are -- some of them can actually really transmit their disease to many, many individuals. But the bottom line comes down to the vast majority do not.

So we needed tools, and that's when we started with smears because we knew those -- we knew those patients who were smear-positive had a higher chance of transmitting. We need tools to identify who really is contagious, especially in places where we have a lot of individuals and especially in places where we have individuals who are immunosuppressed. Expelled into the air. And, again, you have to not only, you know, have TB, but you have to be able to expel these mycobacterium into the air, into airborne droplet nuclei. And as you're aware, as we'll talk about in a second, you know, one of the great things we have is if somebody does have tuberculosis, if you start them on therapy, luckily the drugs we have are highly effective at making patients who are contagious relatively non-contagious relatively fast; you know?

When we look at contagiousness, one of the things I think is important to really appreciate is that it's not just based on how many organisms you have, even though that plays a major role, but also the ability to get the TB into the air, meaning is the patient coughing, and not only are they coughing but how good a cough; you know? Does the person have a cavity in the lung, because, as we know, the person with cavities in the lungs tends to have more organisms and is thus able to produce more droplet nuclei? Does the person have organisms in their sputum because, again, if you can see TB beyond the smear, it means there's a lot of organisms there?

And as we're going to allude to, just because you don't see them on the smear doesn't mean that they're not there, it just means they're a lot less and they tend to be less contagious. Obviously, if you have it in the airways, in the lungs, in the larynx, you're more contagious. And obviously those people who are undergoing cough-inducing procedures are those not getting therapy and those cultures tend to be contagious, but, again, it's not just the smears. You want to see other factors.

And, interesting enough, as much as I told you before that, you know, the original guidelines had recommended three negative smears were really not, at that time, based on, you know, studies that looked at how many. The bottom line is they worked. And thanks to the recommendations of the guidelines in the 1990's, in 1994 and 2005, it is clear that the number of documented occurrences of transmission in congregate settings has dramatically fallen. So we know it's working.

You know, on the other hand, why is this significant? Why do we really care about TB in hospitals? And the reason is, interesting enough, studies have shown that anywhere from 50% to 75% of TB patients are hospitalized for TB. So a large proportion of patients with TB will be in congregate settings. And interestingly enough, about 83% of these hospitalizations is at the time when you make the diagnosis of TB. The good news is from 1995 to 2006, like we talked about before, the number of cases of patients being hospitalized for TB has dramatically fallen from 41%. But here's the problem, even with that, patients with TB spend a significant amount of time in hospitals, anywhere from nine to 17 days. And as you can see, it's quite expensive.

So what are the problems with isolation? You know, why do we really care? Why do we worry about, you know, putting people into isolation? And as we talked about, the problem is we keep people in isolation for a long time, and that takes a lot of resources. First of all, we have a limited number of airborne isolation rooms, places where we can put these patients that John will talk about in a couple minutes.

But here's the biggest issue, and I think most of us know this, there is a risk about putting somebody in isolation. I mean, you know, studies have shown that if you're put into isolation, health care workers tend not to go into those rooms and you get -- you get seen less and subsequently have less care. There's an eightfold increase of number of adverse events in patients who are in isolation. And, interestingly enough, in studies they've done, patients who are put into airborne isolation have a negative perspective of their care.

The other thing is, let's be honest, you can't get a procedure done. If somebody knows that that person is in airborne isolation, it's hard to find a gastroenterologist who wants to go and do an endoscopy. So it delays the diagnosis, especially for patients who don't have TB, and that's the key. Most patients placed into isolation rooms do not have TB. As a matter of fact, some studies have shown that only about one of every 92 patients who -- it's about 92 patients, I should say, you'll find one case of TB. And if you look at all patients placed into isolation, only about 1% to 10% of those individuals placed into isolation actually

turned out to have TB. The vast majority do not. So, again, we know when we test that a find TB, but, more importantly, get people out of isolation quicker so the real diagnosis can be made. But yet we need a test that's sensitive, that can find those cases so that we don't put staff at risk.

So how do we usually do this? As you guys know, we usually do it by three traditional sputum smears. It's usually collected daily. Later on, studies were done because it was recognized that it was taking too long and studies suggested that you don't have to do it once a day but you can do it every eight hours, which is kind of what we're doing right now. But the problem is when you look at it, these sputum smears are still not sensitive. Only about 50% to 90% of patients put into isolation have a positive smear, and it's not specific. As you know, depending on what part of the country you are, about -- like, in Florida, about 30% of our positive smears turn out not to be TB but turn out to be non-tuberculosis mycobacterium. So we need a test that not only can tell who has TB but also, as importantly, who doesn't.

So, back in 2000, when nucleic acid amplification tests were becoming more popular, the CDC put out this guideline to update nucleic acid amplification. And look what they wrote there, they wrote if a sputum smear is negative and the MTD is negative, an additional specimen should be tested. And this was the key. The patient can be presumed not to be infectious if all smear and MTD results were negative, meaning, back in 2000, CDC suggested that if you have two negative MTDs, which was a nucleic acid amplification at the time that was FDA approved, you could be considered non-infectious.

It was because of that specimen that our group in Florida went ahead and did a study using one nucleic acid amplification test, at the time it was the MTD, as compared to three smears to see if we could predict who actually had TB. And as you can see, it was a pretty large study. We took 493 patients prospectively who were put into airborne isolation. Forty-six of them turned out to have TB. And interestingly enough, 40 of the 46 had a positive nucleic acid amplification on the first specimen, compared to only 35 who ever had a positive smear, meaning, you know, of the three they collected, one of the smears would be positive.

So the bottom line came down to that, in our study, neither test was 100% predicting who had TB. Most importantly, though, one nucleic acid amplification could predict who was potentially contagious better than the smear. Again, the PCR was 40 of 46, the smear only 35 of 46. Again, to recognize even with three negative smears, we're not necessarily predicting TB, but we are able to predict who's contagious.

So, subsequently, recently two studies have been done, one that was done out of California, the other one done out of North Carolina, that, again, suggested -- the first study showed that of 139 patients, ten who had TB, if you did a serial smear versus one single GeneXpert, that they were equivocal, meaning that one GeneXpert could predict who was going to have -- who had a positive smear. The other is a study from North Carolina -- I'm sorry, California, of 207 admissions. Again, when they looked at it they, again, found that a single -- or in this case, two PCRs could predict, again, who was going to have a positive smear and who had TB.

And because of that, in February of last year, the FDA changed their indications for the GeneXpert to now include indications for using GeneXpert for the removal of patients on airborne isolation. And if you look in February of 2015, the U.S. Food & Drug Administration approved a change and they, according to their recommendation, stated that negative results using this assay on either one or two sputum specimens can be used -- and I want to emphasize this -- as an alternative to examination of serial acid-fast stained sputum smears to aid in the decision to discontinue airborne isolation for patients with suspected TB. Note that, "to aid in the decision to discontinue airborne isolation," because I want to emphasize something. We're not going to be talking about diagnosis of TB today. We're talking about trying to detect who's infectious while they're in a congregate setting, and utilizing this tool to take people off of airborne isolation quicker.

Again, we must distinguish these communities -- these scenarios because I think we're confusing this in the TB community. We used three smears in hospitals not to diagnose TB alone but, in those cases, to take people off of airborne isolation. This is actually a decision-making tool in this scenario; you know? Now, don't get me wrong, in the process of making airborne isolation decisions, we're still trying to

diagnose TB, but, again, we're utilizing this to take people off of airborne isolation, to find who may be potentially infectious, not necessarily alone to diagnose TB.

So it is a tool trying to predict infectiousness, which, in hospitals, has been traditionally done by three negative smears. And I want to emphasize, because we just don't use smears alone, but the clinical appropriateness of taking somebody off. As we know, even in patients who had three negative smears, if the doctor still feels, if the clinician still feels that the person has TB, that's still important to keep that person on isolation.

So, with that, I'm very proud to -- we're all proud today to be discussing a consensus statement that was put out by the NTCA as well as the American Public Health Lab Association to discuss the clinical applicability of the FDA's, you know, expanded indication for the GeneXpert. And what this represents is a significant document which is meant to be a practical consensus for the -- I'm sorry -- consensus statement for the implementation of the FDA approval for the GeneXpert for airborne infection isolation indications. You know, this is really meant to -- when those came out, the community was really looking for guidance. How do you implement this? And that's what we're going to be talking about today.

You know, I want to emphasize something very important, and then we're going to turn it over. But the bottom line, this is really just a consensus statement. Ultimately, it's going to be up to each state TB program in partnership with the hospital infection control practitioners and other congregate settings of infection control practitioners to set the community standards for the use of GeneXpert for airborne isolation. And the way they're going to do that is by developing the policies and procedures, or some use "Recommended Operating Procedures," it doesn't matter. But ultimately what you're going to do in your state, in your community, is going to be set by the TB community and infection control practitioner community. This consensus statement is really made to try to help the programs and the associations in guiding those community standards.

So, with that, I really would like to move on and really start this program by introducing John -- Dr. John Bernardo. He is a professor of medicine and biochemistry at Boston University. He's also the TB medical officer for the Massachusetts Department of Public Health. He's the NTCA Co-Chair for the consensus statement, and really our leader. And John, we really want to thank you for everything you did. And what John's going to be talking about today is the actual nuts and bolts of the consensus statement. So, John, how's everything up in Boston?

Thank you. I just want to welcome everybody for tuning in. Thank you, Dave, for the wonderful introduction. It's a beautiful day up here in Boston, nice and sunny. Good day for the beach, and it's going to be a fine evening for a Red Sox game where we're playing San Francisco. So thank you, again. And I'm coming to you from Boston Medical Center, the former Boston City Hospital, where one time we had ten patients in airborne isolation for every single patient -- for every one that had TB eventually. So this is an important process. It saves time. It saves money. And as Dave points out, it improves patient care.

Okay. So, to review again, the infectiousness of a TB patient is directly related to the number of droplet nuclei carrying M. tuberculosis that are expelled into the air. It's an airborne disease and the infection is spread when a person inhales these droplet nuclei. Quantitative sputum smear microscopy has been used, as Dave points out, as an index of infectiousness. Microscopy, though, has limited sensitivity and is totally non-specific, and the turnaround time is relatively long. The current practice involves collecting three respiratory specimens, eight to 24 hours apart, and performing smear microscopy on these specimens, again, as Dave went through with you before.

Now, nucleic acid amplification testing was first approved in the United States by the FDA in the 1990s with the Amplicor and the MTD tests that are listed here on this -- that are shown here on this slide. The Amplicor was a PCR-based test that's no longer manufactured. And the MTD is an isothermal amplification ribosomal RNA. It's a relatively labor-intensive test, and it takes time. More recently, in 2013, the GeneXpert was approved by the FDA. It's a PCR-based test. The advantages of these tests are the high sensitivity and specificity for MTB complex, and the relatively quick turnaround time. The turnaround

time for the Amplicor and MTD tests are less than 48 hours. The GeneXpert, though, can give you an answer in two to four hours.

There are disadvantages to these tests. They're costly and they provide no indication of the viability of the organisms or susceptibility to drugs, except for the GeneXpert which reads out a mutation that is associated with Rifampin resistance. And the FDA approval only covers respiratory secretions, sputum or bronchial secretions. For the GeneXpert, only sputum is approved.

The GeneXpert itself is a closed, contained automated platform. The sensitivity is approximately ten times better than that of fluorescent smears at 131 colony form units per ml. And as I mentioned, the turnaround time is relatively rapid. The test uses molecular beacons which are a clever technology that employs fluorescence quenching on the ends of a molecule that hybridizes to the target DNA. The fluorophores are in proximity prior to hybridization and the molecules at the end of the loop on this picture here quench the fluorescence by the indicator molecule. But when they hybridize to target DNA, the molecules separate in space and the fluorescence is no longer quenched, and the system lights up. As Dave points out, these tests were approved -- or this test was approved in 2013 based on several studies, including the one I list here that shows sensitivity and specificity for the GeneXpert in clinical settings.

So, in February of last year, the FDA approved the change to the package insert for the GeneXpert to reflect expanded claims related to airborne infectious isolation. Specifically, it states results using this assay on "either one or two sputum specimens" can be used as an alternative to the examination of serial acid-fast stained sputum smears to aid in the detection to discontinue airborne infectious isolation for patients with suspected pulmonary tuberculosis.

The basis for this labeling change was the improved sensitivity and specificity of nucleic acid amplification versus the AFB smear in the early detection of culture-confirmed pulmonary TB in adults. Negative nucleic acid amplification results using Xpert and other platforms, as Dave reviewed, from one or two sputum specimens are highly predictive results of two or three AFB sputum smears as being negative. And the use of nucleic acid amplification can provide costs savings by reducing patient time and the need to stay in airborne isolation. At the time of the approval of this test indication, the data that the FDA reviewed was unpublished but has since been published and shows the sensitivity and negative predictive value of this test, as I've shown on this slide.

But the labeling change on the package insert did not provide enough details, and we felt it was important to expand on the explanation that was provided in the package insert to help programs and agencies decide how to use these tests more appropriately. So, specifically, we focused on several issues. First was patient selection. The patients for which this algorithm should be applied should be real suspects for tuberculosis. That is, tuberculosis should be a real diagnostic consideration.

Secondly, sputum quality is critical for the diagnosis of pulmonary TB and for the performance of the assay. The assay can be performed on either spontaneously expectorated sputum, which should be representative of the secretions from the lower respiratory tract and should appear purulent. It should not be saliva. Induced sputum, purulence is desirable, but induced sputum may have the appearance of saliva, due to the presence of the saline that is used in the induction process. And then the laboratory considerations where the protocols for collection transport and processing of raw sputum are important to the performance of the assay. And I'd like to emphasize that the nucleic acid test is not a substitute for smear microscopy or culture. The sample still must be submitted for diagnostic purposes.

And lastly, this algorithm and statement is not an endorsement of the GeneXpert. The FDA approval for the use of nucleic acid amplification as a tool to get people out of airborne isolation was approved only for the GeneXpert and not for the other nucleic acid amplification platforms. So that's why this statement is focused on the GeneXpert.

So, within the statement, we inserted protocols for collection of sputum. And this slide shows the process that we indicate in the appendix of the statement to assist programs in obtaining appropriate sputum samples. The patient must be coached and supervised, at least for the first sputum collection. The patient

should understand that sputum is material and is brought up from the lungs, and that nasal secretions and saliva or spit are not acceptable. The sputum should be collected in an airborne isolation room or a negative pressure sputum collection booth, or it may be collected outdoors. And then we list the procedures that should be followed in collecting and transporting the sputum.

The interpretation of the results must occur within the context of the clinical and radiographic presentation and your suspicion for infectious TB. The sensitivity of the test is subject to a variety of factors, including sampling, that is the specimen quality; the appropriateness of transport and processing of the specimen; errors in performance of the assay; and errors in labeling or reporting results are all included in these variables. The results for the test are reported to the requesting clinician and to infection control as either mycobacterium tuberculosis complex detected, mycobacterium tuberculosis complex is not detected, or the test is invalid, that is it failed. And lastly, decisions to remove a person from airborne infectious isolation must not be made in isolation on the basis of a single test or two tests alone. They must comply with local, jurisdictional public health laws and regulations where applicable.

So we put together this algorithm, as you see on this slide. I'm going to take you through it pretty quickly. It involves two steps. And I have to emphasize that this algorithm occurs and it applies independent of sputum smear results; okay? Sputum smears are addressed in the next algorithm I'm going to show you. So you obtain the sputum for AFB smear microscopy culture as you normally would. You do the nucleic acid amplification test, and if it's positive, that is on the left side of this flow chart, the patient has tuberculosis and you should keep the patient in isolation until you determine that he or she is not infectious. If the initial GeneXpert is negative, then you continue airborne isolation because infectious TB is not excluded. If you get an invalid result, again, infectious TB is not excluded and you continue airborne isolation. Invalid results usually mean the assay itself failed and they usually are repeated. So you're seeing two results on the same specimen, but this varies between labs.

If the patient is continued in airborne isolation, you move on to step two. You collect a second sputum at least eight hours after the first for diagnostic purposes and go through the same exercise. If the result on the Xpert is positive, TB is likely and you continue airborne isolation and start therapy as indicated. If the Xpert is negative, infectious TB is not likely and you make your decision to discontinue airborne isolation in conjunction with your clinical criteria at your institution. If the second result in invalid, you continue airborne isolation and use the AFB smear results with the Xpert results, if you have them, and clinical information to make a decision about continuing airborne isolation.

Now, the use of the sputum smear can be helpful here in conjunction with the negative Xpert results, if you have them. So if you have two negative Xpert results, you review the AFB smears. If the AFB smear is positive on two tests, TB is not likely and you most likely are dealing with non-tuberculosis mycobacteria here on the left. If the smear is discordant with the nucleic acid amplification, that is you have one positive smear and one negative smear with two negative NAATs, then infectious TB is not likely but still possible, but you're more likely dealing with non-tuberculosis mycobacteria. If your smear and GeneXpert is negative on two tests, TB is not ruled out and you continue your diagnostic evaluation.

There are some limitations to this process. The FDA-approved application applies only to the Xpert assay performed on raw sputum or concentrated sputum sediment that is prepared from expectorated or induced sputum. It doesn't apply to things like bronchoscopy samples. Importantly, collection of quality sputum samples is critical to obtaining accurate Xpert, AFB smear, and culture results.

NAA testing should not be used solely to determine when a laboratory confirmed case of pulmonary TB can be released from airborne isolation. If you have a diagnosis of TB, the nucleic acid amplification only measures nucleic acid in the sputum. It doesn't give you any indication of viability or infectiousness. And this applies -- this statement only applies to airborne isolation in health care facilities. And lastly, the FDA labeling and approval was based on research investigations of persons 18 years of age and older. I'd like to acknowledge the working group that put together this statement that's shown here. And I'll pass this on to David and the next speaker.

John, thank you very, very much. I really appreciate it, except I didn't appreciate your remarks about the Red Sox. Go Giants. And other than that, we'll be hearing from you in a couple minutes, at the end, as we start discussing some questions. So, John, thank you so much. Next, we're really, really happy to have Dr. David Warshauer. Dr. Warshauer is the chief bacteriologist and deputy director of communicable diseases at the Wisconsin State Laboratory of Hygiene. Dave currently serves on the APHL Infectious Disease Committee and is Chair of the APHL TB Subcommittee.

He has served on national workgroups and has developed the CDC guidelines to be used in nucleic acid amplification testing and detection of TB and for the use of interferon gamma release assays. He was also co-chair with John and Neha on the work group for this consensus statement from the NTCA/APHL. And we are just thrilled to have Dave join us today and talk about the working with your laboratories, some specifics when it comes to the laboratory. So, Dave, how's everything going up in Wisconsin? We're really going all over the map today, huh?

Yeah, we're hot and humid here today. And John, I'm going to be rooting for my hometown Giants, so it's two against one right now. Okay, hopefully I'm unmuted here. So what I'd like to do in the next few minutes is to spend time discussing some of the laboratory aspects about the implementation of the algorithms. Successful implementation requires communication among many members of the health care team, and with the laboratory being a key component.

Now, as John described the GeneXpert system, it's a very useful -- user-friendly system, with minimal manipulation of the specimen required. The laboratorian just has to add sample reagents to the sputum specimen and mix it well, and allow it to incubate for 15 minutes. Then a portion of that digested specimen is pipetted into the cartridge shown here, which is then placed in the instrument for sample preparation, amplification of the target, and detection of that target. And if we're using sediments from specimens that have been decontaminated and concentrated for culture, they're handled in the same manner.

Now, fortunately, the Xpert is a closed system as the cartridges are self-contained, which minimizes the possibility of any cross-contamination and eliminates the need to have three separate areas in the laboratory for testing as it's required for real time PCR assays that are open system. So it allows many laboratories that could not do real-time PCR to -- in an open system, to perform it easily in their laboratory. Now, another plus for the GeneXpert system is that it's available in many laboratories as it's used for the detection of other infectious agents such as Clostridium difficile, methicillin-resistant staph, influenza virus, and many other agents. So the instrumentation may already be available in your institution's laboratory to perform the MTB/RIF assay.

So what are the specimens required for the Xpert? Well, as John mentioned and Dave has mentioned, quality of the specimen is critical, as is getting an adequate volume to perform GeneXpert assay and smear and culture. You know, we have direct observed therapy in TB. I think it's important that we have direct observed specimen collection so that we get the optimal specimens. Now, the Xpert is FDA-approved, as has been mentioned, for expectorated or induced sputum. It's not improved for other specimen types such as broncho lavage or any other body fluids.

Now, the specimen requirements may vary among laboratories. And it's important that these be well-defined and clear to the health care providers using that laboratory. Some laboratories may ask for one specimen of five to ten mils to perform both the Xpert and the smear and culture. Now, this has the advantage of allowing the interpretation of the Xpert in conjunction with the AFB smear result as recommended by CDC. As John described, if you have a negative Xpert result and you know that the specimen is smear-positive, then infection with a non-tuberculosis mycobacterium is likely.

Now, other laboratories may want two separate specimens, one for Xpert with a volume of one to two milliliters and a separate specimen of five to ten mils for smear and culture. Now, these laboratories may have an Xpert system on site in the hospital but have an off-site or reference laboratory that performs AFB smears and cultures. So they don't want to have to split one specimen because, as you can imagine, it can be very difficult to divide up a sputum. And also they want to have an optimal volume for smear and

culture. So they don't want to have to take one to two mils for the Xpert and then have less material for their smear and culture.

Okay. Reporting, as far as reporting, the laboratories are required to report results as directed in the package insert of an FDA-approved test. So this is the verbiage that you should see on reports of Xpert results. And John has shown these, MTB detected, MTB not detected, and invalid. Now, the invalid result occurs when there's a failure of the specimen processing control. This indicates that there may have been inadequate processing of the specimen or that inhibitors of the PCR reactions were present in the specimen. Now, this occurs rarely, only in about 1% to 2% of specimens. And most laboratories will repeat the test using the remainder of the original sample or the digested sputum. And in most cases the retest provides an acceptable result. So it should be rare for you to see an invalid result for the GeneXpert. Now, the Xpert is also able to detect Rifampin resistance, but that's beyond the scope of today's webinar, so we'll go on.

Now, reporting, the report may also include interpretive comments to help the provider interpret the results. And here I show an example of a comment for a negative result. For example, a result of MTB not detected indicates infectious TB is not likely. Make the decision to discontinue airborne infection isolation in conjunction with clinical data. That's just one example for you.

So who do reports go to, and that may vary from institution to institution? So, obviously, the health care provider and infection "preventionists" have to receive reports, but keep in mind the TB control program and local public health departments that also want to be in the loop. Now, many labs have electronic laboratory reporting capabilities which provide reporting as soon as the results are verified and may go to your medical record and to your public health electronic surveillance system.

Turnaround time expectations, and this is really something that's important because we should all be aware of what to expect for turnaround times. The test takes about an hour and 45 minutes, but that is not the turnaround time that should be expected. And it's going to be variable with laboratory -- how the laboratory is structured and how it's staffed. So is the Xpert system on site? Is it at a central off-site laboratory? Is acid-fast smear and culture performed off site? And is there staff available to perform testing on second and third shifts.

Now, the ease and use of the Xpert and the minimal hands-on time required make second and third shifting testing more feasible. If the Xpert system is available on site and raw sputum is tested, the turnaround time may be about two to four hours. If the Xpert system is off site and raw sputum is tested, you have to factor in transport time. Now, if the Xpert is performed in the mycobacteriology laboratory using process sediment, that is sputum that has been decontaminated and concentrated, the turnaround time could be five to 24 hours or more. So it's important to establish realistic turnaround times for your institution and then communicate them to everyone involved in the process. So, with that, I'd like to turn it back to Dr. Ashkin.

Dave, thank you so, so much. We really, really appreciate it, especially you going against the Red Sox. That was great. And we'll be hearing from you in a couple minutes to discuss some of the questions we're getting. And we really appreciate the questions. And please, if you have a question, put it into the question-and-answer section and we will be answering it real soon.

So our last speaker today is Dr. Neha Shah. She is the field medical officer with the Centers for Disease Control and Prevention. She is assigned to the California Department of Public Health currently. Prior to coming to California, she was a TB controller in Chicago and did her EIS training with the Division of Global HIV and TB. She is part of the MDR-TB Consult Service at the California State TB Control Branch. And we're really, really thrilled to -- Neha, we're thrilled to have you, Neha, today. And you're going to be kind of giving us the practical end of the algorithm with some examples. So, Neha, how's California doing? I guess it's still good morning there, huh?

It is morning here. I have my cup of coffee. I'm from Cleveland, so I will have to say I am a Cleveland fan. Although, you know, we have the RNC going on right now, and I will not make a comment on what people think about the RNC. But I'm glad to be here. I hope everyone can hear me okay.

We hear you great, Neha. You're coming through loud and clear. Thanks.

Fantastic. My role here is I'm going to try to walk us through the algorithm a little bit more using some cases to see if we can better understand how the algorithm could apply to individual patients. Just as housekeeping, I don't have any disclosures, and the CDC disclaimer.

I know John introduced the algorithm to everybody. It's probably a lot to look at on your screen. As I said, I'm going to try to walk us through it using a series of cases. As everyone has mentioned, I want us to keep in mind the algorithm is only meant to help us with determining discontinuation of isolation and it is not meant to help us diagnose whether somebody has TB or not. Therefore, these series of cases are going to focus on the question of whether to discontinue isolation or not.

Case one. Case one is a 91-year-old female from the Philippines. He has a remote history of being treated for TB per him in his country of origin a long time ago. He has hemoptysis but no other TB symptoms. A sputum was obtained and was Xpert-positive. The question you are posed with is would you discontinue isolation? Let's look at the algorithm. In this situation where you've gotten a sputum and have a positive Xpert, the algorithm would suggest that TB is likely and to continue isolation. Okay. So that was an easy one. I wanted to build everybody's confidence. Hopefully everyone said they would continue isolation. These are going to get progressively harder, so let's move to the second case.

Case two is an 18-year-old male from China. He has an IGRA that is negative. And a chest x-ray with a left upper lobe calcification and read as consistent with granuloma disease. He's gotten one sputum because his chest x-ray was negative, and it was Xpert-negative. What would you do? Let's, again, look back to our algorithm. And for this situation we would be in the middle row here -- in the middle column where we have a negative Xpert result. The algorithm would suggest that we haven't excluded TB yet, to continue airborne isolation, and continue on to step two which is to collect a second specimen. We get a second specimen and it is Xpert-negative. Now what? Let's go back to the algorithm and to step two. If you have a negative second Xpert, the algorithm would say that infectious TB is not likely. And in terms of discontinuing isolation, you would make this decision in conjunction with clinical data, which could include smears.

Which brings us back to our question, do we discontinue isolation? As a reminder, this individual is 18 years old. He's IGRA-negative. He is asymptomatic. He has a left upper lobe calcification and two negative Xperts. Remember, the question is not whether he has TB or not, but whether we should continue -- discontinue isolation. I'm going to let you guys talk amongst yourselves, as some people are probably with other people. You guys can discuss -- I can't hear anybody, so I'm going to guess you guys are all discussing.

I'm going to go to case three. Case three is similar to case two with a few things that I've changed. We're still talking about an 18-year-old from China. This time, he is IGRA-positive. Still has a left upper lobe calcification consistent with granuloma disease, but has a non-productive cough and is Xpert-negative. Going back to the algorithm, as a reminder, first negative Xpert, what do we do? We get a second specimen. The second specimen is negative as well. Okay. Again, going back to the algorithm, step two, if we have a negative second Xpert result we haven't excluded infectious TB. We can use our clinical data to make a decision of whether or not to discontinue isolation.

Which brings us back to our case, would you discontinue isolation? Again, as a reminder, this is an 18-year-old from China who is IGRA-positive, has a left upper lobe calcification and a non-productive cough. Again, discuss amongst yourselves. I see some people are in the chat telling me what they would do. That's fantastic. And again, since I can't hear you, I'm going to say, based on my running through these slides with a few people here, it's 50/50 whether somebody would discontinue isolation or not, granted there were only two people in the room, but that's okay, still 50/50.

What if I told you he had hemoptysis instead of a dry cough? Would you discontinue isolation then? No. I'm getting people on the chat saying no. Some people are saying no in both cases. Okay. What if it was winter time and I told you this person lived in a dorm and everybody had a cough? It looks like nobody wants to let this guy out of isolation, looking at the chat. But so the point is you could see how this can get a little confusing, depending on the clinical data I give you, as well as what other pieces of information you have.

This algorithm does suggest if you have two negative Xpert results then you can use clinical data to help you decide whether you should discontinue airborne isolation. Some of that clinical data could be smears. So let's say we get a smear on this guy and he is smear-positive? What do we do now? As John mentioned briefly -- introduced us to, there is another part of the appendix that is not directly part of the airborne isolation but will help you interpret what to do with two negative Xperts and smear results when you put them together.

In this case, we have negative smears -- two negative Xperts and a positive smear. Taking all the history and other clinical data together, you could conclude that TB is not likely and it's possible that this individual has an NTM. That's just an example of how you would use these algorithms together. Which, of course, brings us back to our original question, "Would we discontinue isolation?" Two negative smears, dry cough -- two negative Xperts, a dry cough, and one positive smear. And it looks like from the chat, a lot of people would keep this individual in isolation. What I would say is whether you decide to continue or not --- discontinue or continue isolation, always remember to report this to the health department if you are suspicious of TB.

Our last case hopefully will be a little bit more straightforward. This is a 40-year-old U.S.-born individual who is TST-positive. He reports having a minimal contact to a TB case and has a non-productive cough. A chest x-ray that shows minimal infiltrates in the right middle lobe and has gotten a sputum which is Xpert-negative. Again, going to the algorithm, if you have one negative Xpert, you would go on to step two to get a second specimen. Our second Xpert was positive. And in this situation, if you have one negative, one positive, we would put it in the TB is likely and to continue airborne isolation.

In summary, concluding from all of us talking today, historically we've used three smears to determine when to discontinue isolation. Now we can use Xpert results. The consensus statement was developed to assist with determining criteria based on Xpert for when to discontinue airborne isolation. As mentioned throughout these presentations, you should not use the consensus statement as a diagnostic algorithm. If it smells like TB, it's still TB.

So, for example, if you suspect somebody has TB because they're a close contact, a smear-positive individual who had a large cavitary lesion, and that individual was coughing on your patient, it's probably still going to be TB, even if you have some negative Xperts and you have a chest x-ray that shows a cavitary lesion. Lastly, keep in mind -- keep the public health department programs aware of any suspected TB cases, even if you have negative Xperts. If you still think TB, please let public health departments know. That's it from my end. I will turn it back over to Dave.

Neha, thank you so much. Really, really appreciate it. You know, I think it's always interesting, you know, when you're looking at the actual cases. And we -- you know, I think that one of the key points we're going to really talk about is, you know, how is this going to apply, how are we going to go forward? And I think one of the most important things, because I'm looking at some of the questions. I'm going to start going over them right now. But I think one of the big questions is, like, who's going to take the lead here.

You know, one question that was posed to us which is one -- and I'm going to turn to the panel -- but, you know, the question was, "Is there any talk of the CDC changing their infection control guidelines to reflect these new -- the expanded indication by the FDA?" And, you know, at least I'm not with the CDC, and Neha, I'm not so sure. But, you know, the bottom line comes down to I'm sure there's going to be a new incarnation, like there always is. I mean, one thing about the CDC, they've always updated it. But the

question is we're not so sure when that's going to happen, if I'm correct, you know. Dave or John or Neha, anything you want to add to that?

No. This is John. When we first thought of doing this, we talked with the CDC about it, and they felt that what we needed was a consensus statement to assist programs in using this at this time. So they had no plans of jumping into this at this point in time.

So, exactly. So, I mean, I guess the question -- the next thing is, well, how does this get implemented? Let's be honest, when it comes to, you know, hospitals, usually what happens is these get implemented by infection control, you know, practitioners in a facility. Each hospital usually has their own infection control committee, and they usually base how they take somebody off of isolation. It's usually based on community standards. And most community standards are usually based on recommendations and also policies of, you know, organizations. And now with the idea of the consensus statement was really to try to help local TB programs, local infection control practitioners to start to develop how were they going to handle airborne isolation based on the new FDA expanded indications as well as based on new research. John, do you agree with that? Neha?

I think that's accurate -- this is Neha -- and that different institutions will implement it based on discussions with their infection control practitioners and their local health departments.

Right. I mean, already in Florida, we're seeing our major hospitals start to implement it. And just to give an example, in the State of Florida, we are planning, as the TB program, to put out a policy that essentially says that, you know, this is an acceptable alternative or protocol to three smears, with the intention of trying to improve on both the detection of who has TB as well as who doesn't and who could be taken off isolation. And we're hoping, at least in the state, that once we do that that our local Florida infection control practitioners will follow. And, you know, I think it's just one of these things on -- I think it's a ground roots operation where our TB programs take the lead in conjunction, in coordination with our infection control practitioners in the community and our partners in congregate settings.

You know, which brings up a question that we're getting is that -- you know, we talk a lot and it's interesting, almost all of these studies have been done in hospitals, but there are other congregate settings that see patients with TB. I think most notably is our correctional facilities. And, you know, the question is how do these recommendations, John, from your perspective, how do they apply to correctional facilities?

Well, the FDA approval itself was restricted to health care facilities. So how individual institutions interpret this is up to them. The data are the data. The data are strong enough to support the use of this test for this purpose, regardless of whether you're in a correctional institution, clinic facility, or in a nursing home or an inpatient facility. So it's really up to the local infection control group as to whether to use this or not for this purpose. Again, this is a guidance statement. It's not a guideline, per se.

Neha, Dave, you want to add to that? Neha, how do you feel about how it would be -- in your community, how would it be applied to corrections?

I think it's a very good question and one of these areas that's a little bit in a gray zone because there are potentially two settings. There is -- in the corrections system where there are clinical or hospital types of bed aids, you can use it as you would in any other health care setting. But in terms of releasing to the general population, you know, this consensus statement wasn't really meant as a way to understand how to release to the community. Surely there can be some application, and I would leave that to each individual program to understand how to apply it to their setting. But that was not necessarily how the FDA labeling was done. But, again, I think it can be interpreted probably with some help with your ICP.

Yeah, I totally agree, Neha. I mean, I think you'd agree, we always, when we're dealing with our correctional partners, we're always kind of looking a little closer at, you know, before we take somebody off of isolation, especially if we're going to put them into a general population, we really want to make sure that the person truly doesn't have TB. And we may be a little more cautious, but, let's be honest, at this

point we're still using smears. And if anything, the studies do show that the GeneXpert, even one GeneXpert is at least as good as the smears, if not better. So I think, just like you said Neha, I think, you know, it's going to be to the local -- you know, to the local organizations and those people who make decisions who know their population best.

Talking about kind of, you know, populations and stuff, we have actually a really interesting question, you know, about actually -- about what happens if the first Xpert is invalid. So the participant that asked is -- and John, I think this is really towards the protocol question. "If the first GeneXpert is invalid and the second Xpert is negative, then" -- you know, the question is, by some interpretation, maybe seeing that infection is not likely because that second one was negative again, but I think if the first one is invalid, are we supposed to go back to the beginning again and get -- you know, go through getting two more? What -- how do you interpret if the first one's invalid, John?

Well, it's addressed in the footnote, we just didn't have time to go through the details. But if you look at the algorithm, the footnote really addresses this. If the result of the second one is negative following an initial invalid result in step one, and infectious TB is still clinically suspected, a repeat test, that is repeating step two using a new specimen, if available, is recommended. And that's basically just to improve the sensitivity of the process.

Alternatively, the clinician might use the single negative Xpert result from step two with smear results and clinical information to make a decision to continue or discontinue airborne isolation. Remember, the FDA labeling change says one or two negative Xperts. One of the reasons we went into this was to try to provide a little bit more detail into that. So I think we covered these things. If you read through the statement itself and look at the algorithms in detail, it's in there.

You know, John, you're right. You know, if you're looking at the performance, you know, you made the statement before that, you know, in some ways, you know, you have the choice of one or two. And, you know, we got a question from San Diego, and it's a great question. The question is, in San Diego, they're saying that they have never seen -- if they have a negative, you know, GeneXpert on the first assessment, they've never seen a case -- and, again, I'm not -- but they've never seen a case where the second one has added to it. And yet, you know, like in our study or in others, you know, depending on how much TB you have, like the study that was used to make the -- to look at this, there was one of the six cases that they used only one GeneXpert, they would have missed it but the second one picked it up. And I guess the question comes down to, I think a lot of how well these -- this test and any test performed is really based on the prevalence of the disease in the population, and that's where some local -- you know, if some local -- you know, basing your recommendations on local epidemiology is important. Neha, John, do you agree?

Yeah. This is John. We also added to the statement that local programs should record their data and analyze it to assess the appropriateness of the algorithm itself. This is a work in progress; you know? The approval was based on limited but generally reproducible and generally -- I won't say "generalizable data," but, as you say, findings vary between communities. So we invite programs to maintain and analyze their own data on this, and adopt a protocol to their own situations locally. Neha?

Yeah, I would agree with what you both are saying. We do live in a low prevalence country and that will, of course, affect how a test performs. So I would agree with you. In addition to what Dave was saying in terms of the laboratory quality of specimens, so there are several different variables at play here that can affect how these results work. And I agree. I would encourage people to look at their local data after they've implemented Xpert to get a sense of what their results look like.

And talking about getting -- you know, getting a look at what their results look like, you know, Jon Warkentin in Tennessee brings up the interesting point, which is that, in Tennessee at least, there is really not a lot of GeneXpert, or at least the penetration is not really done there yet. And the question is, but a lot of hospitals are using their own PCRs. And I guess the question comes down -- and I'm going to put this to Dave -- you know, what's the use of other platforms, besides GeneXpert, for maybe how we would be utilized in this algorithm?

I think -- at this point, I think the laboratory would have to take a look at their test to see what its sensitivity is with smear positives. How does it compare to three negative smears -- or three smear results, and do a validation that, yes, their test performed similar to Xpert where you get similar or better results with a negative PCR, in this case maybe a laboratory-developed test or another one of the commercial tests, and validate their test performed well enough to be used in this algorithm.

And Dave, I think that would be a validation that would be done by the lab itself; is that correct?

Yeah, I think in -- it would be helpful to, in conjunction, possible with some institutions where you have -- where your -- you know, a public health laboratory may be serving many hospitals and working with the infection "preventionist" in those hospitals and getting data from them on smears, on culture results that they may not have would be very helpful in trying to validate their assay for this purpose.

While we have you up, there's also a question about are there any infection control considerations for lab personnel handling the specimens for the GeneXpert or running the GeneXpert?

Well, running the GeneXpert can be done at a BSL2 laboratory. You should be handling these specimens in a biosafety cabinet like you would if you were setting up a sputum for a routine culture or processing it for a mycobacteria culture. The sample reagent I mentioned is a solution of sodium hydroxide and isopropanol. So the treatment of the specimen with that reagent, if there is TB present, will not maybe -- well, will not sterilize it, but will reduce the viability in infectiousness of that specimen. So it's a very safe procedure, but I would recommend doing the work in a biosafety cabinet in a BSL2 laboratory.

Thanks, Dave. Thank you very, very much. You know, we're running out of time, so I really want to just put a bunch of questions together. And so there's a number of questions about what about the use of GeneXpert for taking people off of isolation? The first question is, like, how long does the GeneXpert stay positive and do you wait for a GeneXpert to be negative to take them off of isolation? Neha or -- well let's start with John, I mean, just because I want to -- I want to just harass him as much as I can. John, what's the use of GeneXpert in the -- to take somebody off of isolation?

Yeah. Once you have a diagnosis of tuberculosis, you have a diagnosis of TB. The Xpert and the other platforms just measure nucleic acid. They don't give you any indication of viability of the organism. So there's no place for the use of nucleic acid amplification for monitoring somebody who has a diagnosis of TB. Once you have the diagnosis, you have it.

As a matter of fact, Neha, I think you'd agree, once of the downsides of using nucleic acid amplification is in patients who had TB prior. I mean, I've seen nucleic acid amplifications positive for years after the person has been diagnosed and treated and cured of TB with no clinical symptoms. I think you'd agree, Neha, that one of the difficulties is interpreting a positive nucleic acid amplification in somebody who had TB before when making the, you know, the decision to take somebody off of isolation. How do you feel about that?

Yeah, I would agree with you and John in that once you have a diagnosis of TB, really, circling back to this consensus statement, it doesn't apply at that point anymore. You have a TB patient. You have a diagnosis of TB. We're not really talking about the consensus statement at that point. There are other guidelines to think about when you can release somebody who has been a diagnosis of TB, who had smear positive, and when to let them out of isolation after treatment, so on and so forth, but that's different from using the Xpert consensus statement. But definitely, I agree in that once you have a diagnosis of TB, you don't really want to use the GeneXpert to help you determine how someone his progressing.

Neha, I think you'd even agree, like, even if -- not only just a diagnosis now, but, you know, we had situations where, you know, we had somebody from eight, nine months ago who, you know, who completed therapy, and now they have hemoptysis, you know, maybe from NTM or bronchiectasis. They get admitted into respiratory isolation and the nucleic acid is positive. So I think nucleic acid amplification

in those kinds of situations are helpful if they're negative, but maybe difficult to interpret if they're positive and the person had a history of TB, especially in the, you know, the remote past.

Definitely, and that can be confusing because they can stay positive for quite some time but be culture negative.

And, you know, Neha, while I have you, I mean, the other issue, I mean, we're getting a lot of calls -- a lot of questions on is where do smears work into this? You know, I think there's a little bit of confusion about, in the past, you know, when we used to talk about nucleic acid amplification, there used to be those requirements that you would only run it on positive smears. And there's a lot of questions of, like, how do you -- you know, would this be better if you did it on people who had positive smears. Is there any role for using -- you know, when it comes to taking somebody off of isolation, is this an alternative or should it be used in conjunction with smears?

So I think that's a very good question, and we struggled a lot when we put this consensus statement of how to incorporate smears into the algorithm, or where to incorporate them. And really, when you look at the FDA label, they're kind of the separate entities when you're talking about discontinuation of isolation. In general, you know, what the CDC guidelines suggest is that everybody should -- every TB case should have at least one NAAT done. It is certainly helpful with smear-negatives that you -- if you can get a positive NAAT, and I would encourage people to do them on smear negatives, especially if you are considering TB. But yes, the yield is obviously a lot higher on your smear-positive, but you're already going down that route of thinking TB on your smear-positive, too. So it's helpful for both, but I don't think it's -- they're not intertwined when you're looking at the FDA label on airborne isolation, but it can help you when you're still thinking of TB and you have negative Xperts.

John, anything to add to that?

No, not at all. The algorithm itself operates independent of sputum smears. The second algorithm addresses the sputum smear. As Neha says, this is different from diagnostic testing. This is testing to determine if it's okay to take somebody out of airborne isolation or not.

I totally agree. I think that's really the take-home message. Recognize that, you know, again, smears are helpful in diagnosis. Nobody's saying not to do, you know, smears, but it's different. This is really in the determination of taking somebody off of airborne isolation. Hey, last question and then we're going to have to run. But Dave, I'm going to end up with you. The question is what about the availability of GeneXpert, you know, do you see more institutions getting GeneXpert and, if so, why? And so if you wouldn't mind just briefly maybe your experience or your thoughts on that.

Yeah. I'm seeing a lot of the smaller laboratories, medium-sized laboratories going to the GeneXpert because of its ease of use. And it has a very wide range of agents that it can be used for in the laboratories. So I have seen, at least in Wisconsin, a very slow uptake of the MTB-RIF assay. And part of that may be because in Wisconsin we provide testing at the state laboratory that's fee-exempt, and many of the hospitals use our services for NAAT testing. But the -- you know, there's over 10,000 GeneXpert systems out there. You see them more and more in U.S. laboratories. So I think the capability is out there for a lot of labs to institute the MTB/RIF assay in their laboratories.

Yeah, I agree, Dave. I mean, in Florida, we're seeing more and more hospitals picking it up, and, again, not for TB, they're picking it up for the other organisms that they can rapidly detect. And from a TB perspective, that may be very, very helpful because as more facilities are getting the GeneXpert platform for other organism detection, they'll be easier for them to implement the TB RIF, you know, recommendation.

Right, if they don't have to make an investment in an instrument, it's much easier and economically feasible to implement the test.

Well, I -- we're running out of time. So I want to stop here and I want to first thank our panelists. I want to thank Dave, Neha, and John, not only for this webinar but for putting the consensus statement together. And as John alluded to, I want to really, really thank the whole panel that really worked on it to get it done. And I also -- I can't say that without -- I want to thank the leadership of the NTCA and the American Public Health Laboratories for putting this out there to help the TB community, to try to make these very, very difficult decisions and utilize resources better. Again, as TB is declining, less and less patients have TB, and it's more and more important to detect those that do and, most importantly, get the ones that don't off of isolation so we can get the appropriate work-up.

Most importantly and lastly, on behalf of the panel, we want to thank all of you out there, again, for doing everything you do to fight TB, detect TB, and for definitely listening to today's discussion. And I'm very happy. I'm going to be turning over to Kelly. But in one week, we're going to have the second part of this webinar, which is really going to be much more clinical, discussing actually scenarios and practicalities. So, with that, Kelly, I want to turn it over to you. And, again, we hope and wish all of you to have a great day, great week, and great summer. Kelly, it's all yours.

Okay. Wonderful. Thank you. Thank you, again, to NTCA, APHL, and all of today's presenters. This concludes today's webinar.