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AACC Practical Recommendations for Implementing and Interpreting SARS-CoV-2 EUA and LDT Serologic Testing in Clinical Laboratories

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Guest: Dr. Victoria Zhang is the vice chair for clinical enterprise strategy & associate professor at the Department of Pathology and Laboratory Medicine at University of Rochester Medical Center, where she also serves as the chief of the clinical chemistry division.

Bob Barrett: This is a podcast from *Clinical Chemistry*, sponsored by the Department of Laboratory of Medicine at Boston Children's Hospital. I'm Bob Barrett.

The clinical laboratory continues to play a critical role in managing the coronavirus pandemic. Numerous FDA emergency use authorization kits, and laboratory-developed tests serologic assays have become available. The performance characteristics of these assays, and their clinical utility continue to be defined in real time during the course of this pandemic.

The American Association for Clinical Chemistry convened a panel of experts from clinical chemistry, microbiology and immunology laboratories, the in vitro diagnostics industry, and regulatory agencies to provide practical recommendations for implementation and interpretation of these serologic tests in clinical laboratories.

The AACC COVID-19 Serologic Testing Task Force's practical recommendations for implementing and interpreting SARS-CoV-2 EUA serologic testing in clinical laboratories appears in the September 2021 issue of *Clinical Chemistry*.

The lead author of that report is Dr. Victoria Zhang. She is the vice chair for clinical enterprise strategy & associate professor at the Department of Pathology and Laboratory Medicine at University of Rochester Medical Center, where she also serves as the chief of the clinical chemistry division.

So first of all, Dr. Zhang, tell us about the background for this guidance, and why did AACC put this task force together?

Victoria Zhang: Yes. Hi, Bob. Thanks for the question. First of all, I think even at a very early stage of the pandemic, it became apparent that the clinical laboratories will continue to play a very critical role in managing the pandemic for both the diagnosis and monitoring. I also wanted to mention that very early stage of the pandemic, and numerous emergency use

authorization (or EUA) and laboratory tests, LDT serology assays have become available.

So also, because of the EUA process, the performance characteristics of these assays and their clinical utility continue to be defined in real-time during the pandemic. So frankly, and to be honest, I had to research what EUA meant at the time when I first heard it. And not alone to imagine how to utilize this implement in the laboratory.

So, the two areas that discussed most: of course one is molecular testing analysis serology. So, for this one, we're going to focus on serology testing. So, many questions are raised in the community about the assay, how do we use it, and how to implement that, and also interpret the results. So, for AACC as the authoritative organization for clinical chemistry, we have done a tremendous amount of work throughout the pandemic. One thing we feel that the serology testing and also some clarifications on this test was another area that we could contribute to the community.

So, that was kind of the big background when we started to talk about and formed task force for COVID-19 serological testing tasks force within AACC. That task force was formed in April 2020. So, it really to address the ever-increasing questions on the utility of the serology testing for COVID-19. And also, I wanted to share that we took a couple steps: the first effort for the group was to actually publish a public statement. We thought we're going to take an approach that can have a very quick turnaround time, so that the community can raise the awareness of the utility and the limitations of the serology testing.

So, I had to give kudos and recognition for the task force. We actually worked tirelessly for one month, and published a public statement, AACC recommendations for serology testing in May 2020. And also, shortly the after that, we felt that the task force can do a little more and more in-depth guidelines for this testing, not just utility, not just implementations. Actually, you know what, validations; how do we do this? And also, overall quality management. That's kind of big several steps, and the big background that we had for the task force.

Bob Barrett: And what are the highlights of these newly published guidelines?

Victoria Zhang: Well, there are several. First of all, I wanted to mention that, actually, we picked very closely the title of the document, we call that "Practical Recommendations" because we felt like we still know so little about the virus. I think the team feel a little bit uncomfortable calling it a guideline when it can change back and forth.

But overall, I'm just saying, a guideline isn't easy to refer. Everybody referred this as a guideline. I just wanted to make that caveat to know that we were actually very quite careful when we picked the title of the document. So that being said, I think we would think, this is one of the guidelines we can come up with at the time that we know the virus.

So, in terms of the highlights, I'll mention a few things. One is that, the team. The team that's involved for this guideline. Not just like, we have experts in clinical chemistry, we have experts for microbiology, and immunology, and we have people from academic hospitals, we have people from reference labs. We also invited the experts from the IVD industry who are actually making the products for the assay. And on top of that, we also have a lot of regulatory agencies. So, the idea is that, for the guideline can have as much input as possible from as many different angles as possible. So, that's one.

I think the group had to really review the current literatures, and also, I think provide their first-hand experience and expert opinions, because the thing is, we even a bit in this moment, we know only so little about this virus, and you're not alone about a year ago. So, when we first put this together, so searching we would like to know all of those who put the input as much as possible from all different angles. So that's number one, I'll say, the team.

Secondly, is the content. I'm very proud of the comprehensive content of this document. We do have two versions: one is they're going to be published on *Clinical Chemistry* that is an abridged version. We also have a full and more in-depth version that's available on the AACC website, and that's freely available to everybody.

So, I'll say in this guideline we provided as a number one the most up-to-date understanding of host immune response to SARS-COVID-2, and also the associated antibody kinetics, and also, the available assay EUA. Actually, I reviewed that again, just yesterday as those are still relevant. I know there are still things you evolve, but I think the overall picture, the immune response, and the antibody kinetics are still relevant for what we have now, are still good reference.

On top of that, we have the clinical utility, assay limitations, and we also discussed to help the laboratory to select the appropriate assays for their use, and the targeted populations. And also, the guideline was it discussed I think extensively, the process and considerations that are necessary to verify or validate either UA or LDT serology tests in a laboratory setting. In addition test interpretation, and

orthogonal testing, and also the laboratory safety that are involved are also outlined.

So, I think, although there are various organizations that have published guidelines on clinical utilities of serology, I do feel like our guideline is, I think, this is the first, and the most comprehensive document related to the laboratory professionals. How do we make it happen in the laboratory to implement the test? And also, to interpret the results.

The last highlight is that we also have in mind that for future outbreaks. As being said, when the team put together, we're trying to, one, is really specific to COVID-19, but on the other hand, we are also trying to make that as general as possible, particularly in the implementation and validation for the assays to see what's going to happen in the laboratory if we have the outbreak?

We hope this will be a good reference when next time it happens, I don't hope that's going to happen, but I think it will, right? This is also not the first time. It's just one of the biggest epidemics that we encountered, but certainly, this is not the first, and I don't think that's this going to be the last.

Another highlight is that, we're really having in mind the team to have this as a use for reference for future outbreaks.

Bob Barrett: Doctor, how do you hope that laboratory professionals will use this guidance?

Victoria Zhang: Also, based on the highlights I just mentioned, previously, I think there are few ways I hope the laboratory professionals can use this guideline. Number one, use of this as a general reference for current understanding of host immune response to SARS-COVID-2, and also in antibody kinetics and a summary of available UA assays. At the time of publication, there are certainly several more added, but we certainly have a lot of important features that listed for those assays. I hope those still be of use to the laboratory professionals.

Another one is, utilize this guideline to understand the clinical utilities and limitations of serological testing, so that in addition, I hope they can get insights into the nuances in implementing the UA or LDT serologic testing in clinical laboratories. I think another one is to appreciate the challenges in interpreting serology results.

We also have several example reports included in the guideline. I hope that will be of use to people who are thinking about how do they report the results, and we have some discussion about orthogonal testing. I think we're one of the few who discussed this in the guideline. I hope that also can be of use to the laboratory professionals.

Bob Barrett: Well, let's flip our outlook right now, what about the recipients of the test results? How do you hope that clinicians or interested patients will use this guidance?

Victoria Zhang: Yes, that's a very good question, Bob. Certainly, we had the clinicians and the patients in mind. It is a different community that we have to think carefully. Number one, I hope either clinicians or patients when they review their results, hopefully, after reviewing this guideline they are going to be more careful when they read the results, so that they can be aware, and understand the limitations of the testing. So, serology testing is not recommended for diagnostic purposes for SARS-COVID-2 infection, and that that's number one.

Number two is that, I hope they are aware that having antibody is a great thing for anybody, but also, we still don't know the correlation between the antibody levels and the protective immunity of the virus. So, we still needed to be cautious.

We have a lot of disease that can be protected by vaccines, as we know, like Hepatitis B, but usually when it comes to vaccines and a virus, that's also a very important question to ask is they identify the level, maybe the minimum allowable, Minimum antibody allowable that are required for protecting immunity for the virus. So, at this moment, we still don't know that level yet. So, I hope recipients, and clinicians, and patients after they review this guideline, I hope they can take this wisdom when they review their results.

Bob Barrett: How do laboratory experts expect physicians to use these tests in the future? What kinds of questions are clinicians asking now? And how do you see that evolving?

Victoria Zhang: I think number one, is that, we still don't have a consensus in terms of how to use serology testing now. I think that's the key issue for serology testing, right? There's some potential usage. I can see, for instance, like a vaccine booster or re-vaccination of people, and they are asking the key question is that, the relationship between the minimum level of antibodies required for protecting immunity, and also how long the protection level will remain in our system?

I think until we know that, we really need to be cautious when they interpret the antibody levels, and serology tests. Hopefully the physicians can keep that in mind when they read the results. And also ask questions, right? Clinicians certainly continues to look for answers from the laboratories.

Also, one of the silver linings of the pandemic is that, it certainly put the laboratory and laboratory professionals, I

think more than ever, into the spotlight for what we're doing for healthcare. So, I mean, we've been getting some of the common questions, what I hear also from my colleagues, such as, from physicians, like, should we the order the tests for their patients, right? Why has this patient tested negative after vaccine or sometimes even COVID-19 had the disease? And at what that means.

What happens if a patient is immunosuppressed? We will continue to have those questions, and I also see that, the questions are going to evolve in the future as more as, what do the variants mean, right? How do we handle the variants? And also, as of the now it's summer, the fall and winter is going to come, how are we going to handle with this, and the flu in the winter? Are we talking about the boosters? Are we talking about group vaccinations?

I can say that, we're really watching history in the making, and we will get more and more clear answers to those questions as we learn more about that novel virus. We really look forward to continue to work with clinicians and physicians to tackle this pandemic.

Bob Barrett: Well, finally, Dr. Zhang, as we record this interview in late, July 2021, just under 60% of all Americans have received at least one dose of the Coronavirus vaccine, how can an antibody tests be used to assess people post vaccination?

Victoria Zhang: There is limited usage for antibody at this point for post-vaccination, and we still have a lot of questions, but no answers. However, I think one thing that is clear as that, the protective function of vaccination. We still have questions about the nuances as how much level we need to get to get protected? How long we're going to be protected? But I think, one thing is clear, that is, having a vaccine has the protective function.

So, I want to give the round of applause for the ones who already received their vaccines, and they are really using their action to help our community fight this pandemic. I'd also take this opportunity to urge the community to really focus on getting vaccines. I hope we will continue to increase the rate of population that receive vaccinations. I think, that's really a very important step for our community to fight against this novel virus.

Bob Barrett: That was Dr. Victoria Zhang from the Department of Pathology and Laboratory Medicine at University of Rochester Medical Center. She has been our guest in this podcast, on "AACC's Practical Recommendations for Implementing and Interpreting SARS-COVID-2 Serologic Testing in Clinical Laboratories." That report appears in the September 2021

issue of *Clinical Chemistry*. I'm Bob Barrett. Thanks for listening.