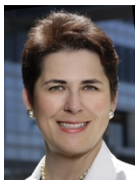
Coagulation tests and COVID: inside labs, industry

January 2021— *COVID-19 and coagulation testing were up for discussion on Nov. 20 when six people joined CAP TODAY publisher Bob McGonnagle to talk about that and laboratory labor, relationships with industry and hospital administration, and the distribution of testing. "We're working with all the manufacturers to support rapid point-of-care testing to manage hot spots that will pop up once there is a vaccine," said Orchard Software's Curt Johnson.*

With Johnson and McGonnagle on the call were Oksana Volod, MD, of Cedars-Sinai Medical Center; Neil Harris, MBChB, MD, of the University of Florida; Annie Winkler, MD, MSc, of Instrumentation Laboratory; Nichole Howard, MBA, of Diagnostica Stago; and Jason Lam, MBA, MLS, of Siemens Healthineers. Drs. Volod and Harris are members of the CAP Hemostasis and Thrombosis Committee.

The CAP's guide to coagulation analyzers begins here.



Dr. Volod

Dr. Volod, the coagulation findings that have come out of early investigations of COVID have been interesting. What is top of mind for you as you think about coagulation and coagulation systems? What's most important?

Oksana Volod, MD, director, coagulation consultative service, and associate professor of pathology, Cedars-Sinai Medical Center and David Geffen School of Medicine at UCLA: The good quality of the reagents and the assays available and the quick turnaround time, and potentially new assays that I can bring in-house quickly during this COVID period, specifically assays for fibrinolysis. As you said, there are the specifics of COVID coagulopathy, and now they are pointing out that fibrinolysis shutdown is one of the elements of the COVID coagulopathy. However, only the reference laboratories would have this type of testing. So we are validating fibrinolysis assays on our instruments.

Dr. Harris, are you also seeing a rise in demand for this particular assay?

Neil Harris, MBChB, MD, clinical professor and core laboratory medical director, Department of Pathology, Immunology, and Laboratory Medicine, University of Florida: Yes, we're seeing a rise in demand for D-dimers and also coagulation factors, especially factor VIII. We used to run factor VIIIs mostly during the day, except in emergencies, and now we are running them around the clock.

The other thing I'd like to point out, and it's something we have discussed at meetings of the CAP Hemostasis and Thrombosis Committee, is that a number of clinicians have said to me they have certain criteria for D-dimers, but in fact there are different units for D-dimers. For COVID management, as with other situations, there hasn't been a standardization of D-dimer units.

Dr. Winkler

Dr. Winkler, can you give us your reaction to what you've just heard from the pathologists? And can

you relate that to your experience at Instrumentation Laboratory in the past year?
Annie Winkler, MD, MSc, VP of reagent R&D and medical affairs, Instrumentation Laboratory: Our first priority is, and has always been, to make sure we can support our customers in these challenging times, as it not only puts challenges on them but also on us in our manufacturing facilities. We're also investing in the future to better understand and help identify additional markers so we can bring the most innovative solutions to the market. It's been a time of extensive literature review, working with talented investigators, looking at new markers, and even exploring some of the synergistic, nontraditional laboratory hemostasis analyzers, such as our ROTEM system and its applicability as a point-of-care whole blood test for hemostasis.

Nichole Howard, can you, too, give us your reaction to what we heard from Dr. Volod and Dr. Harris?
Nichole Howard, MBA, product manager, instruments and customer experience, Diagnostica Stago: We're seeing the same thing. We're seeing the increase in factor VIII and in D-dimer, and I can follow what Dr. Winkler said in terms of our focus being on manufacturing, to make sure we have the right products in the right place at the right time to meet customer demand, and on looking at how we can work with our customers to make sure they're adopting reliable strategies.

Jason Lam, I'll let you round out our panel of instrument and coagulation vendors with comments of your own.
Jason Lam, MBA, MLS, U.S. marketing manager, hemostasis, Siemens Healthineers: Siemens Healthineers has done the same. As soon as COVID hit and we started to see an increase in D-dimer—it was before the white papers started to come out and we even knew it was happening, we saw it happening with our volume uptick in orders—we right away went into manufacturing to ensure we did not go into any backorder situations. We wanted to make sure that the physicians and the labs could provide those results without interruption. The increase in D-dimer usage was exponential, less so for factor VIII.

We worked closely with our clinical affairs team for a full understanding of COVID—we have the chemistry portfolio too—and started to release educational information, because we're all learning together. It was and still is an amazing event to be a part of. Everyone is trying to help patients by developing new assays and markers.

Curt Johnson, tell me from your perspective, or if you'd like to relate it more specifically to coagulation, what kind of operating burden COVID has placed on your customer laboratories and the laboratories you're calling on.
Curt Johnson, chief operating officer, Orchard Software: Speed and timely information are paramount, even more so than in the past. We've always said the product of the laboratory is information, but it's information in the hands of a provider to improve patient care. When a pandemic hits and everyone is learning at the same time, from an information perspective, we have to have the capabilities for and compatibility with the new analyzers and reagents that manufacturers are developing, to make sure we understand those parameters and can respond quickly.

For the different types of D-dimers with no standardization yet, we have to have the flexibility to handle all the different attributes of the testing labs are doing, and as they're creating tests, be able to capture that data and have it available to be dissected and analyzed to improve patient care.

As new analyzers come out, perhaps a new point-of-care testing analyzer, we have to understand the output from that analyzer, how it will be integrated into the LIS, to ensure the information gets to where it needs to go. As the testing moves closer to the patient, the workflow changes, so it becomes important that the software works hand in hand with the analyzers to improve the providers' experience and to improve patient care.

From a COVID point of view, everything sped up. Everybody needed to expand their LIS capabilities. They needed to expand their reagents, their volume, plus how they were going to distribute and use the information. We have been working with different state and county departments of health, ensuring that they have the information they need and making sure the laboratory scientists have the necessary data to allow refining of their test menus and workflows.

Dr. Volod, D-dimer is a well-known assay but one that has not always been well understood, particularly by some clinicians. Has COVID led you to additional consultation with clinicians, and talks about D-dimer with some physicians, that are a little out of the ordinary for you?
Dr. Volod (Cedars-Sinai): As Dr. Harris said, D-dimer units have been a hot topic among the CAP committee members, so I've been dealing with that topic for several years. Based on that, I take a more proactive approach at Cedars. First, we wanted to make sure our assay meets certain criteria. Our physicians—specifically the emergency department—wanted to switch to age-adjusted D-dimer. So I looked into the assay, comparing it to the major studies done on the age-adjusted D-dimer.

We've been dealing with the clinicians and D-dimer for three or four years. And then when COVID hit, our system had a series of lectures on COVID coagulopathy. We have daily updates for certain groups. We have a task force, and we were giving hospitalwide web-based talks on COVID coagulopathy. One of the first was on COVID coagulopathy from the laboratory perspective, where I went through the first data from China and said, "These are the units we're using, and we need to make sure we are comparing those units to the units we are using." So from the beginning I brought our doctors onto the same page—what we are using, what that measures, how that compares to the published data. More than 500 physicians attended the first talk I gave.

I do provide coagulation consultative service. Clinicians can either order a test or a panel related to COVID coagulopathies. And I'm in constant communication on this subject.

Is there now a better understanding and use of the D-dimer test at Cedars-Sinai?
Dr. Volod (Cedars-Sinai): Yes, but I was surprised. D-dimers are part of our COVID assessment protocol. When a patient comes to the institution, my expectation was that a serial D-dimer would be done. What I'm noticing is they order an initial D-dimer level, and that's it. But you need to see a progression, where a patient is moving with his coagulopathy, if it is worsening, and I believe D-dimers play an important role in it. So my work here is to encourage them to do a serial level and to provide them meaningful feedback on the results.


Dr. Harris

Dr. Harris, can you give us the trajectory of understanding the coagulation tests that need to be used in a COVID case?
Dr. Harris (University of Florida): We've mostly relied on our benign nonmalignant hematology group. They've taken the lead in guiding the other services through the COVID coagulopathy. They have drawn up guidelines and protocols for anticoagulation and what to measure, particularly D-dimers. We don't have the panels available as such, but D-dimer, factor VIII, and fibrinogen appear to be, for better or worse, the main analytes they're looking at.

There has been interest among our cardiovascular anesthesiologists in viscoelastic testing, which I know Dr. Volod is involved in. Although we use the viscoelastic testing, we haven't used it at all in the COVID cases.

So our model has been to let the clinical hematology group take the lead, and we take our guidance from them, as far as the testing goes. So far we haven't seen supply chain issues with the coagulation testing, though we've seen many issues in other areas of the laboratory, particularly microbiology and virology, even for non-COVID tests.

Dr. Volod, can you give us a brief overview of where viscoelastic testing is and where it's going?
Dr. Volod (Cedars-Sinai): I'm a strong believer in all viscoelastic assays. All of them provide important information in the right settings. Thromboelastography and thromboelastometry are similar technologies. Next-generation

technologies such as the TEG 6s by Haemonetics and Quantra by HemoSonics are FDA-approved, cartridge-based point-of-care systems. We have the TEG 5000 [Haemonetics] and TEG 6s. One assay is not superior to another. They are all helpful. However, I was surprised that our team doesn't have much interest, unfortunately, in ordering it more frequently for COVID patients. I almost insisted that they at least let us see a few patients with COVID coagulopathy, and they sent about 10 patients. The patients were on heparin because our protocol from the beginning was if these patients were admitted with COVID, they should be on heparin prophylaxis. I didn't see them being that hypercoagulable. I had a few patients who were not on anticoagulation from the beginning, and they were significantly hypercoagulable.

So they are assays that give you a global assessment of all the hemostasis in one assay testing whole blood of the patients, versus conventional assays. There is a certain advantage. With this type of testing, we potentially can see if fibrinolysis is present or absent. With the several publications about fibrinolysis shutdown in a group of COVID patients, it's another layer that viscoelastic assays potentially can add. However, the TEG 6s version just started to have the fibrinolysis parameter as a part of the cartridge. Both the TEG 5000 and ROTEM Delta [Instrumentation Laboratory] can assess fibrinolysis. And I think HemoSonics still validates fibrinolysis on the cartridge. But there has to be more information—how to use it, how to interpret the results—and there is still no standardization between those assays.

Dr. Winkler, can I get a comment from you on that topic?
Dr. Winkler (IL): As Dr. Volod said, there are several different viscoelastic systems with many similarities and some differences. For several centers, we've seen growth of ROTEM testing with COVID, and we're sponsoring a multinational clinical trial to further investigate the coagulopathy of COVID with ROTEM testing, on both ROTEM Delta and Sigma platforms.

Howard

Nichole Howard, early on there was a falloff in the demand for many standard clinical laboratory tests, as they relate to elective and other procedures, and then we went through the period, which I don't think is over, of patients being reluctant to come into clinics and hospitals for testing. How have you seen this up and down of demand over the past few months as it's reflected in your work at Stago?
Nichole Howard (Diagnostica Stago): We did see ER and ICU beds being the focus, and there were mass cancellations of routine and elective procedures. Then, as things started to come back, the laboratory had to maintain its COVID testing but also ramp up and try to deal with the backlog from the cancellations as patients started to return. We've seen a steadying of that.

We talk to our care networks about the importance of having diversity in the type of instruments and type of setting. For instance, using a smaller automated platform in a clinic setting, rather than a point-of-care device, to measure PT/INR, where you get a comprehensive treatment of the patient. Let's say the patient is going in to get their PT/INR done. They are able to get the result they need at that time that they've been out of the house. There's no risk of their having to return to be redrawn or having to go somewhere else to get a laboratory test performed. By keeping those patients close to home in smaller settings that are separated from COVID patients, it's building the confidence that they're making sure they're taking care of their regular checkups that are fundamental to being sure we don't add stresses at other points in the health care continuum.

Jason Lam, tell me about what the ups and downs have been of demand for tests and where you think we are now. Are we back to normal? Are we back to 90 percent of normal?

Jason Lam (Siemens Healthineers): Back to normal—I smile, because is anyone normal now? When the D-dimer volumes were going up drastically, we also saw routine testing drastically decline, and it was happening fast.

It started to come back but routine testing is still affected. As you shut down routine labs and start running the testing only in some of the larger hospitals, volume capabilities are becoming increasingly important. Hospitals want to know whether they can take on more volume without having to replace current instrumentation. That's making these facilities re-evaluate when they bring in new instruments and whether they are bringing in the right fit with the ability to grow quickly. Economically, with the routine hospitals shutting down, it does come down to financing and how they are able to get the equipment into their facilities.

I'm seeing a lot of change in the market, at least from acquisitions of instrumentation, partnerships, and how they are doing the hub and spoke of the independent network hospitals.

Johnson

Curt Johnson, you have a good feel for how systems are working, with centralized flagship hospitals but then in clinics, doctors' offices, and the important smaller hospital that is under siege in nearly every respect. Tell us about this health system environment and the testing within it.
Curt Johnson (Orchard): The challenge we are seeing now in the reference labs that are associated with the large institutions or large IDNs that have their own core labs is: How do I ramp up the volume for COVID testing along with the other tests I need to do? At the same time, if you have a nursing home or senior living care facility within your organization or as a client and you are the expertise they rely on, some of that testing needs to move out into those organizations. So point-of-care testing is moving not only toward the patient within the hospital, but also out of what we would consider traditional laboratory space. How do you get everything connected in that scenario?

The question is: How will this process change when the vaccine is widely available? We're working with all the manufacturers to support rapid point-of-care testing to manage hot spots that will pop up once there is a vaccine. We believe that the high volumes of COVID testing won't substantially go down by this time next year, but that testing will expand dramatically in different settings, and that shift will take place throughout all of health care. As we move to a more preventive care, value-based model, while the cost per reportable might be higher for low-volume point-of-care analyzers, the cost to the whole episode is dramatically lower, and we believe that's where the need for information and testing will shift. So we're preparing for both the high volumes we're seeing now and the disbursement and distribution in the future.

Dr. Harris, do you, as medical director of the core laboratory at UF Health, have a few thoughts about how the distribution of testing will be affected by the experience we've had in the past year? And do you have personal views about what would be most desirable?
Dr. Harris (University of Florida): The core laboratory was never much involved in virology until about a year or two ago when we started doing more virologic tests, and that happened to coincide with the pandemic. So this has become a main thrust of the lab, but I don't think it has affected the coagulation that much, but there's been a restriction of the workforce—a move of the staff to the COVID testing. There's a shortage of people on the bench.

Prior to the pandemic, we had a number of specialized tests available. For many years we've been running the anti-Xa assay for unfractionated heparin and low-molecular-weight heparin. We have assays available for some of the newer oral anticoagulants. So thus far, we haven't had to introduce new assays.

I agree with Dr. Volod that viscoelastic testing is important. I had mentioned earlier that our nonmalignant

hematology group has taken the lead in guiding the hospital. At the moment, though, most of the interest in the viscoelastic testing has come from anesthesiology and the intensive care unit.

In terms of COVID, although we do many viscoelastic tests, it has not yet become a mainstay or main criterion for assessing the COVID hypercoagulable state at our institution. The nonmalignant hematology group has used the more traditional methods, and by that I mean the D-dimers, factors, and fibrinogen.

I'd like to talk about the lessons we may have learned over the past year and how they might shape the future. I'll give you an example. Many for years have promoted Lean, standardization on one standard analyzer, not wanting to keep excessive reagents or supplies on hand. We wanted just-in-time scheduling. And that has caught many labs short, not just for COVID testing but for other testing, as has been pointed out. Nichole Howard, are you seeing a shift in the planning philosophy among some of your customers?
Nichole Howard (Diagnostica Stago): Even in our personal lives we're seeing a lot of people do this. We wouldn't have run short on toilet paper throughout the year if that were not the case. But you make a good point. When it comes to things like D-dimer, anti-Xa, yes, our customers are wanting to have more of a sort of security blanket. We've worked with our customers to determine precisely what they need and to build confidence. We've been happy that no one has gone into backorder. For us, the focus has been on education and confidence-building for the customer, that we can make it through this and don't need to stockpile. We're worried about the collective health, so we're each doing our part to take the things we need and not stockpile.

I don't see customers turning away from being lean. In fact, the need to play catch-up on canceled elective surgeries and things of that nature, and the shortage of people on the bench as Dr. Harris said, may have reinforced the need for lean work environments, the right care pathways, and making sure you have the right tests onboard. A good example is anti-Xa and not using the PTT to monitor heparin. I think it makes the laboratories stop and reflect on how to partner most strategically with their vendors to be sure they have the right tests at the right time for any patient.

Lam

Jason Lam, same question—what are the long-term implications, and what are you hearing directly from customers as they're planning for next year?
Jason Lam (Siemens Healthineers): Things came to a halt last year; future planning was delayed. We have all come to find that COVID-19 will be with us for the foreseeable future. Hospitals, labs, will have to continue to be lean because of the economics of all those routine surgeries and everything else going on. They don't have a choice but to be lean in their solutions going into the future.

I can't predict if it changes the mindset of how we move forward as a health care system, but I can tell you that over the past six months, the partnership and communication between the manufacturer and the hospital facilities and medical directors only grew stronger because we as manufacturers heard what was needed and were able to deliver. The FDA cleared tests quickly to meet these needs through emergency use authorization. D-dimers were always available, heparins were available. I hope the partnerships and collaboration continue in the future.

Dr. Winkler, would you like to comment?
Dr. Winkler (IL): I agree with Nichole and Jason regarding the partnerships. We've seen that as well. We are working closely with our customers and have been able to be there for them, sometimes on site if applications teams were needed to assist with installing or helping to validate new tests.

The other thing that has come up is automation for coagulation, which historically has been behind other areas of the laboratory. As the workforce may be challenged, the question is what is the opportunity for increased efficiency with automation and hemostasis.

That's an important point, and I'm going to ask Curt Johnson to comment on it. Lately, I've been hearing a lot of worry about staff burnout and staff shortages. At first, quite a few people were furloughed and now they're recruiting retired technologists and others, trying to bring them back into the laboratory. Curt, how do you see the labor issue affecting us going forward?
Curt Johnson (Orchard): Pre-COVID, the value of the laboratory was never fully understood. The value of laboratory information in health care and in treating patients is astronomical compared with the cost, yet the lab does not normally get the recognition it deserves—until we started seeing press conferences on the White House lawn and the president talking about point-of-care analyzers and the volume of daily testing. As we move forward, I think the country will notice the value of the laboratory, and when you have a spotlight on the laboratory's value, you may see more people interested in joining the force.

Now in the interim: For the past 25 years we've had a labor shortage in the lab. Between the scientists, the diagnostic companies, the automation, and the information systems, we have managed to offset labor by automation, and I think you will see that continue.

Dr. Harris, we know historically that public diseases and problems like AIDS and hepatitis have had an effect on willingness and desire to go into the laboratory field—I'm talking now of technicians, phlebotomists, and medical technologists. Do you fear a similar effect from COVID?
Dr. Harris (University of Florida): I've actually been encouraged, even prior to COVID, by the number of young people we've been getting in the lab—certainly not enough, however. But when I first started in Gainesville in 2002, 2003, there was a large cohort of medical technologists who were about to retire, and the prediction then was that there would be no replacements ever. I think there has been a growing interest in it.

To some of the points others made, yes, the status of the lab has been elevated by the testing available during the COVID crisis, and I think there is a growing interest among graduates in laboratory medicine.

In my own situation, we've had a much better relationship with the hospital administration regarding equipment and support. This is surprising because a few years ago I would never have predicted it.

But the crisis in terms of the staff shortage is far from over. We are chronically understaffed. We use travelers—people who are semi-permanent, going through the lab. I wish there were more medical technology programs throughout the country. A number have closed over the years. I'm hoping that this current situation could reverse that.