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Restricted information, see page 3

COMMENTARY & OPINION by...

R. Lewis Dark
Founder & Publisher

Helping Labs with Cash Flow, COVID-19 Response

Routine specimen volume remains down by 50% or more for clinical laboratories and anatomic pathology groups in the United States because of the pandemic. Through the end of last week, The Dark Report estimates that labs in the U.S. have lost almost $7 billion since the first week of March. That's when patients stopped visiting their doctors and hospitals ceased admitting patients for elective services.

This is a financial disaster without precedent in modern medicine and the clinical laboratory industry. Many labs and pathology groups may not survive much past the end of the SARS-CoV-2 outbreak. Over the past eight weeks, The Dark Report has been in the forefront of documenting these developments and guiding pathologists and clinical lab administrators on effective strategies, winning responses, and opportunities to deliver more value to the hospitals, physicians, and patients they serve daily with vital lab testing services.

But we are ready to do even more for you and your lab team! Today, we launched *COVID-19 STAT Intelligence Briefings* at the URL: *https://covid-19briefings.com*. This is a free service, which will deliver to you daily information that is actionable and that you can use immediately to keep your lab or pathology group at the front edge of COVID-19 testing services in a financially-sustainable manner. You'll get timely intelligence in these four areas:

1) Metrics on key aspects of rapid molecular testing and serological testing for COVID-19 (including rates of positive and negative test results), presented in dashboards provided by leading companies in lab billing/collections, lab analytics, and lab-specific CRMs.
2) Proven steps for labs to introduce and validate COVID-19 tests, (both rapid molecular tests and serological tests) and have confidence that the results are accurate, reproducible, and high quality.
3) Latest developments on getting paid for COVID-19 testing to ensure every lab's financial stability and clinical quality.
4) Legal and regulatory updates for labs doing COVID-19 tests to ensure full compliance.

For 26 years, we've worked hard to provide you with valuable management insights that improve patient care and bolster your lab's financial performance. In this crisis, count on us to go the extra mile on your behalf! TDR

FDA Replaces March 16 Serology COVID-19 Rules

Before issuing new guidance on May 4, the FDA okayed more than 200 tests, some were fraudulent

CEO SUMMARY: In the rush to allow companies and clinical laboratories to develop, validate, and bring to market serological tests for COVID-19, the federal Food and Drug Administration issued rules on March 16 that eased its requirements for these new assays. Because of the lack of oversight under the March 16 rules, the market was flooded with tests, including some that were unproven and some that were fraudulent. On May 4, the agency reversed course and issued more rigorous requirements.

On March 16, the federal **Food and Drug Administration** (FDA) issued rules allowing lab-test manufacturers to market COVID-19 serological tests with little or no agency review.

Yet, on May 4, just seven weeks later, the FDA issued another set of rules that essentially replaced the earlier rules with more rigorous requirements that test developers must meet to register their COVID-19 antibody assays and obtain emergency use authorizations (EUAs).

When it issued its March 16 policy, the agency said it was granting "regulatory flexibility for developers offering such tests without FDA review and without an EUA." Test manufacturers only needed to notify the agency that they had validated their serological tests and provide disclaimers about the limitations of the tests. "The FDA does not review the validation or accuracy of the data for these tests unless an EUA is submitted," the agency stated at that time.

Without any meaningful oversight, the FDA was flooded with notifications from test manufacturers ready to offer serology COVID-19 tests to labs and providers. At one point in early May, the FDA had listed more than 200 COVID-19 serology tests submitted under the March 16 rules. However only about a dozen of these tests obtained an EUA, according to published reports.

The rules issued on March 16 caused a cascade of problems, including the introduction of faulty and fraudulent tests that were not approved or authorized, but rather were introduced without review.

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Following the FDA's easing of rules requiring agency review for COVID-19 serology tests on March 16, criticism came from clinical pathologists, lab administrators, and others who said the rules would allow substandard serology tests to flood the market. That flood of unproven tests established "a wild west show" in the market, said Eric Blank, DrPH, Senior Director of Public Health Systems and Programs for the **Association of Public Health Laboratories**. "It really has created a mess that's going to take a while to clean up," he told the *Associated Press*.

Confidence in Test Accuracy

Regardless of whether tests undergo FDA review, clinical laboratories are responsible for validating the performance of all tests they provide. However, because the FDA was allowing these serology tests into the market without appropriate regulatory review, laboratories lacked the data to give them confidence the COVID-19 serology tests they were buying would produce accurate, reliable, and reproducible results. Would lack of FDA review, and the data it publishes after it reviews a test, affect how these laboratories evaluate and select COVID-19 serological tests?

At all levels in the healthcare system, the goal in early March was to encourage new COVID-19 antibody tests to quickly become available in the market. The FDA was under pressure from the administration, members of Congress, and the public to speed up the process of getting diagnostic tests for COVID-19 developed and into clinical use.

Pressure to Acquire, Validate

But any rush to push new diagnostic tests into clinical use has significant implications for clinical laboratories. These labs were under equally intense pressure to acquire, validate, and offer large numbers of COVID-19 serology tests to physicians and patients as soon as possible.

Facing an obvious and pressing need, FDA officials thought the most important goal was to get more tests onto the market quickly, according to published reports. At the time, clinical laboratories were introducing the reverse transcription-polymerase chain reaction (RT-PCR) test—considered to be among the most accurate ways to detect the SARS-CoV-2 that causes the COVID-19 illness. But those tests were coming to market slowly after the federal **Centers for Disease Control and Prevention** botched the introduction of the first RT-PCR test that it offered to labs.

Then, the FDA required manufacturers and clinical labs seeking to run these RT-PCR COVID-19 tests to submit requests for EUAs before they could run these tests. While the agency okayed many of these requests, review came slowly, often taking a few days but sometimes stretching out for several weeks.

Meanwhile, government scientists—including members of President Trump's Coronavirus Task Force—stressed that the nation needed serology tests designed to identify antibodies for the virus. They urged labs to validate COVID-19 serology tests quickly so they could perform these tests in volume.

Recipe for Failure

But as with so many processes in clinical lab testing, moving quickly and eliminating rigorous review of new COVID-19 serology tests is a recipe for failure, clinical lab experts told THE DARK REPORT. *(See, "Expert Offers Comments on FDA and Revised Serology Test Rules," on Pages 6-7.)*

Following weeks of criticism, the agency changed course, issuing new guidelines on May 4. When it announced the new rules, the FDA said the regulations it issued in March led to criticism and the need for more rigorous standards on commercial test companies, as well as the need to crack down on fraudulent test manufacturers.

In commenting on the May 4 rules, the FDA said all serological test manufacturers would need to apply for an EUA, and all tests would need to have at least a

90% level of sensitivity to detect coronavirus antibodies and have a sensitivity level of 95% to avoid false positive results.

Also, on May 4, the agency assured the public that it would act against companies that do not follow the new rules. "We have and will continue to take appropriate action against firms unlawfully marketing their tests," the agency wrote. It would do so, for example, by detaining illegitimate test kits at the border and refusing to let them into the country.

Faulty Serological Tests

In addition, the FDA said it is educating states and healthcare systems about the need to be vigilant about faulty tests. "If particular commercial manufacturers that are currently marketing tests under our March 16 policy fail to submit an EUA within 10 business days, we intend to share this information publicly," the agency said. "We will keep up our work to stop illicit tests from entering the U.S., and we encourage states, hospitals, and consumers to be on high alert and to make informed purchasing decisions regarding these tests."

Under new guidance the FDA issued on May 4, the agency required all developers of serological tests for the novel coronavirus to submit requests for EUAs.

Also, the agency said test developers needed to submit validation data within 10 business days from the date they notified the FDA of their validation testing or by May 14, whichever is later. The agency also set performance standards for specificity and sensitivity for all serology test developers.

In addition, the FDA said, each high-complexity lab developing a laboratory-developed test (LDT) to identify antibodies for the coronavirus must have a valid CLIA certificate from the federal **Centers for Medicare and Medicaid Services** to develop these serology tests. These labs also will need to notify the FDA about the results of their validation studies and meet other labeling recommendations that the agency issued in its March 16 policy. "Developers of LDTs are still encouraged to seek authorization through an EUA," the agency concluded. TDR

—Joseph Burns

FDA Explains Why It Issued New Test Rules

IN A STATEMENT THE FEDERAL FOOD AND DRUG ADMINISTRATION published on its website on Monday, May 4, the agency explained the reasons it needed to change the regulatory review process for serological tests for the novel coronavirus.

"In mid-March, it was critical for the FDA to provide regulatory flexibility for [COVID-19] serology test developers, given the nature of this public health emergency and an understanding that the tests were not to be used as the sole basis for COVID-19 diagnosis, a fact that remains true today," the FDA said in a statement, titled, "Insight into FDA's Revised Policy on Antibody Tests: Prioritizing Access and Accuracy."

"However, flexibility never meant we would allow fraud," the agency added. "We unfortunately see unscrupulous actors marketing fraudulent test kits and using the pandemic as an opportunity to take advantage of Americans' anxiety.

"Some test developers have falsely claimed their [COVID-19] serological tests are FDA approved or authorized. Others have falsely claimed that their tests can diagnose COVID-19 or that they are for at-home testing, which would fall outside of the policies outlined in our March 16 guidance, as well as the updated guidance," the FDA said.

"Also, since that time, the FDA has become aware that a concerning number of commercial serology tests are being promoted inappropriately, including for diagnostic use, or are performing poorly based on an independent evaluation by the NIH," said the agency.

COVID-19 Update

Expert Offers Comments on FDA and Revised Serology Test Rules

Tougher rules issued on May 4 show FDA's concern about faulty or fraudulent COVID-19 serological tests

CLINICAL LABORATORY DIRECTORS are asking what caused the federal **Food and Drug Administration** (FDA) to issue a highly questionable policy in March to allow serological tests for SARS-CoV-2 and then change that policy seven weeks later.

Under a policy the agency issued March 16, the FDA granted what it called "regulatory flexibility for developers offering such tests *without FDA review and without an emergency use authorization*." *(Italics by TDR.)*

No Agency Review of Tests

Under the modified rules of March 16, test manufacturers were simply required to notify the agency that they had validated their serological tests and provide disclaimers about the limitations of the tests. The agency added, however, that "The FDA does not review the validation, or accuracy, of the data for these tests unless an EUA is submitted."

In the ensuing weeks, the market was flooded by more than 200 COVID-19 antibody tests. Some of these tests were faulty and others were fraudulent, according to published reports.

Many lab professionals questioned why a federal agency known for its often-rigorous review of lab tests and other medical devices could be so lax about serology tests in the midst of a pandemic.

"The reasoning FDA gave on March 16 for allowing COVID-19 serological tests without review was the simplistic notion that these tests are less complex than molecular tests," commented Roger D. Klein, MD, JD, a former adviser to the FDA and a faculty fellow at the **Center for Law, Science and Innovation** at the **Sandra Day O'Connor School of Law** at **Arizona State University**.

"Further, FDA stated that because serologic tests have limited usefulness for diagnosis, the agency assumed the tests would be used primarily for epidemiologic purposes," added Klein.

"This explanation isn't wholly satisfactory, however, because serology testing performed for epidemiologic purposes doesn't require FDA authorization," continued Klein. "In addition, the potential of using serology tests as a surrogate for immunity to COVID-19—which could permit some individuals to safely return to work—has been a topic of discussion for some time.

Surrogate for Immunity

"This additional potential use—the serology test result as a surrogate for COVID-19 immunity—should have been apparent to the agency," he commented.

"I suspect FDA's March 16 policy was in part a reaction to the FDA's role in delaying the introduction of diagnostic testing early in the epidemic, for which it has been widely criticized," Klein added. *(See, "Regulators Acted Slowly as Labs Developed Tests for Coronavirus," TDR March 30, 2020.)*

Next, Klein addressed why the agency changed its policy for review and clearance

of COVID-19 serological tests on May 4 to require test manufacturers to withdraw their serological assays or seek emergency use authorizations for these products.

"It's likely that FDA did not anticipate a flood of serology test products, many of which are from China and other Asian countries and some of which are of questionable quality," Klein explained. "It appears that significant numbers of COVID-19 serology tests were introduced from marginal foreign manufacturers."

But why did the FDA take so long to address this situation? "The reason the FDA reacted when it did was probably for several reasons," he noted. "It's likely the agency recognized some of these tests were of dubious quality, and in part it was a response to news reports in major media outlets that raised questions about many of the 200 or more tests offered without review. As well, some of those news reports cited a study that appeared to highlight some of the poor or uncertain performance among some of the tests.

Use in Non-CLIA Lab Settings

"Plus, FDA intended for serology tests to be performed in CLIA-certified laboratories, but some companies used them outside CLIA settings," Klein added. "There were also cases where certain manufacturers falsely claimed that the FDA authorized their COVID-19 serology tests for use."

The FDA's new policy announced May 4, could generate a significant amount of work for the agency, he said. "It could raise new concerns about how long reviews will take and whether there will be significant delays in getting tests on the market."

As of May 8, the FDA had approved emergency use authorization for 12 of the original 200 or more serological assays and listed 116 of those tests as "Not FDA Authorized." It was not clear if the manufacturers had withdrawn the remaining assays.

Klein noted, however, that all of the test manufacturers were supposed to have validated their tests prior to offering them. Therefore, they should have already done that work before the FDA does its EUA review, which should help shorten the time to authorization, he added.

Properly-Validated Tests

"Also, the number of submissions may be far less than the numbers of tests currently offered," Klein said. "Most of the reputable manufacturers that properly validated their serological tests will submit their data to FDA. However, those companies that did not fulfill these basic requirements may not respond at all.

"I expect the legitimate manufacturers that validated their serological tests and provided validation summaries and performance specifications to customers will submit their data to the FDA under the new rules," Klein commented.

"If they do, then it seems likely such tests will continue to be legally sold after submission and before final review, unless FDA sees red flags or other potential risks in specific tests," he added. "For these companies, the review times need not be long because so much of the necessary work has been completed.

"Some manufacturers—and perhaps even a large percentage of them—will not submit data to the FDA," Klein said. "And, I suspect that some sellers in this group may even continue to sell their products here illegally.

"It should also be noted," he continued, "that FDA has already granted EUAs to about a dozen or so tests from reputable manufacturers with acceptable or even excellent performance. That means clinical laboratories currently have multiple choices when deciding which serological test for COVID-19 they want to use."

Pathologists and clinical laboratory managers can expect to see continuing news headlines about serological testing because of the need to test large numbers of individuals to determine if they have been infected with COVID-19. TDR

—Joseph Burns

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Legal Update

New Lab Revenue Source: COVID-19 Worker Screening

CLINICAL LABORATORIES have a new revenue-generating opportunity, as some states relax stay-at-home rules: Many employers are likely to seek COVID-19 screening tests for employees returning to work to detect the presence of the new coronavirus.

This new source of lab specimens and revenue gives clinical labs an opportunity to replace some revenue lost since early March. That is when routine daily specimen volume began to fall by as much as 60% for most labs. *(See TDR, Apr. 20, 2020.)*

Doing COVID-19 testing for employers is new work. It is totally different from the routine clinical testing ordered by physicians. But with routine specimens and revenue down by more than half, a growing number of clinical laboratories recognize that this new source of test referrals could at least partially help offset lost revenue and help the lab maintain financial solvency during the pandemic.

However, the opportunity to replace lost routine test volume with COVID-19 screening tests for employers brings some legal risks that need to be considered and planned for by labs performing such tests, according to Richard S. Cooper, a partner with the national firm of **McDonald Hopkins**.

"In recent weeks, we've been asked by a growing number of clinical labs about the legal issues associated with performing COVID-19 testing for employers who want to screen their employees for this disease," explained Cooper. "There are important steps a lab should take to mitigate the risks it might incur as a result of testing for COVID-19 on behalf of an employer.

"When an employer requests a lab to test its employees, there are additional risks that must be addressed, compared to standard COVID-19 testing," he noted. "Both the lab and the employer establishing testing for employees returning to work need to understand and address these risks.

"Employee screening will become very prevalent and will continue to be a part of COVID-19 testing because many employers are requiring these tests as a screening process before workers are allowed back into the workplace," said Cooper. "Employers need to limit the possibility that infected employees can infect the on-site workforce. Employers also have certain legal obligations to ensure a safe workplace."

Mitigation of Legal Liability

As clinical labs work with employers to implement such testing, they should be aware of the legal liability mitigation in two areas. "First, labs need to have contracts with employers that appropriately limit risk," he advised. "Second, employers and labs need to make employees aware of the purposes and limitations of such testing, and those employees need to sign testing consents.

"For example, no tests are perfect, and so a clinical lab needs to disclose that information to the employee being tested," he added. "Remember, any test can produce a false positive or false negative and COVID-19 screening test result shows the employee's status for that moment. That's why it's important to qualify what the test does. In other words, the lab gives a result at a specific point in

time. That result may not be valid the next day and the employee needs to know that.

"Every lab should take several steps as it begins working with an employer establishing a COVID-19 testing program for its employees," stated Cooper.

"First, the lab needs to make it clear to the employer and to the employer's workers that the COVID-19 testing is for screening purposes only to determine if the employee can return to work," he noted. "The lab is not providing a diagnostic test to the employee.

Not a Patient Relationship

"Second, the lab needs to make it clear that it is not establishing a patient relationship with the employees being tested," he continued.

"The fact that these two disclosures are made—hopefully in both the contract with the employer and in the disclosure consent forms that employees sign—would be important in terms of defending a claim of professional liability," said Cooper.

"Third, your lab wants to inform the patient that the laboratory will provide results to both the patient and to the employer," Cooper warned. "This is not true in a in a normal clinical testing situation where a lab reports test results to the patient's physician, but not to the patient's employer. In fact, in a diagnostic setting, under the Health Insurance Portability and Accountability Act (HIPAA), reporting a test result to anyone but a patient and the patient's physician would likely violate HIPAA.

"But, because this COVID-19 test is for screening purposes, the results obviously need to go to the employer," he continued. "Therefore, in this situation, the lab needs to also disclose the test results to the patient. That's because the results will be used for the purpose of determining whether the employee can return to work, meaning the test result will affect that worker's ability to re-enter the workplace. That's why your lab needs to disclose this information to the patient."

When a lab wants to ensure that it's protected in such a situation, there are several issues to consider. "Typically, when a lab does a COVID-19 screening test for an employer, it's best to have a contract with that employer," Cooper said. "The contract would explain clearly what the lab will do and what the lab's responsibilities are versus the employer's responsibilities. Outlining each party's responsibilities is a top priority when drafting a contract with an employer.

"In the contract, the lab might want to add that the employer will distribute a patient consent form to employees who get tested," Cooper commented. "That consent form is designed to cover any of the exposures that the lab and the employer could face.

"In that form," he continue, "the lab would explain that it is doing this screening testing on behalf of the employer. It would also be wise to require employees to complete a health status questionnaire the day of the testing. If the employee indicates that he or she has any COVID-19 symptoms, he or she should not report for testing.

Consent Forms

"Also, the contract will need to have some language that clearly states that the employer will obtain the requisite consent forms from each employee," Cooper explained. "That means the lab can prepare those forms, but the lab could have the employer be responsible for getting the signature of each employee.

"Another element labs should include in the contract is a clear statement that the employer is responsible for complying with all state and federal employment laws regarding screening tests, including requirements from the federal Equal Employment Opportunity Commission (EEOC)," he said. "Those requirements address employee health and safety, and so may relate to employee testing." TDR

—Joseph Burns

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Consistent Method Used to Evaluate Different Serology Tests

Calif. Research Team Analyzes Performance of 12 Serology Tests

CEO SUMMARY: Researchers with the COVID-19 Testing Project used a multidisciplinary effort to analyze and compare the performance of 12 serological tests. One finding is that, 16 to 20 days or more after a confirmed infection with a molecular test, many of the 12 serological tests analyzed were 80% positive. Using donated blood samples, the researchers assessed the volume and number of antibodies the SARS-CoV-2 produced in infected patients.

From mid-March until May 4, manufacturers launched more than 200 serological tests to identify the antibodies patients produce in response to infection from the new coronavirus.

The performance of these tests was mostly unknown because the federal **Food and Drug Administration** (FDA)—under the rules it issued on March 16—allowed almost all of these 200 tests on the market without the usual review. Without performance data except from the manufacturers themselves, clinical laboratories followed the *caveat emptor* principal of buyer beware when choosing among these tests for clinical use.

The FDA reviewed the performance of only a select few of the tests that applied for the FDA's emergency use authorizations (EUAs) before May 4, when the FDA issued new guidance for serological tests for SARS-CoV-2, the virus that causes the COVID-19 illness.

Seeking to fill the gap in performance review, a team of researchers analyzed the performance of 12 of the serology tests in a significant effort to do a comparative review to benefit clinical laboratories, public health officials, patients, and clinicians.

The researchers provided a significant contribution, because the FDA's March 16 policy for serological tests provided what the agency called "regulatory flexibility for developers offering such tests without FDA review and without an EUA." Test manufacturers were required to simply notify the agency that they had validated their tests, and they needed to provide disclaimers about the limitations of the tests. Additionally, the federal agency added that, "The FDA does not review the validation, or accuracy, of data for these tests unless an EUA is submitted."

Emergency Use Authorization

As of May 7, the FDA listed the performance data for only 12 serological assays that had received EUAs and yet, according to published reports, the agency's website listed 200 or more serological assays that were approved for sale in the United States.

The regulations on March 16 were intended to make it faster and easier for test manufacturers to bring tests to market to track the SARS-CoV-2 pandemic. As a result of requiring little in terms of supporting performance data, test manufacturers flooded the market with tests, some of which performed poorly, produced inaccurate results, or were fraudulent.

In response, on May 4 the FDA issued new rules requiring all companies seeking to sell serological tests in the United States to apply for EUAs. According to a review of FDA data on May 8, 116 were no longer authorized and 12 had received EUAs. The FDA site made no mention of what became of the other antibody tests, suggesting that the manufacturers may have withdrawn them from the market. *(See "FDA Replaces March 16 Serology COVID-19 Test Rules," pages 3-5.)*

Researchers Step Up

In the seven weeks between the FDA's March 16 decision and the May 4 revised policy on antibody tests, there was no accepted, industrywide standard for a high-quality COVID-19 serological assay for labs and pathologists to use for comparison. Therefore, the team of researchers from two universities and two bioengineering companies in California decided to develop a way to compare the performance of 12 serological tests on offer. In April, the researchers published their findings online.

The lack of performance data had created a pressing need for an independent body to produce a consistent method to evaluate the performance of serological tests for the SARS-CoV-2 infection, said Patrick D. Hsu, PhD, an Assistant Professor and Faculty Fellow at the **University of California, Berkeley**. A bioengineer and geneticist who normally works in genome editing, Hsu is one of the researchers leading the multidisciplinary COVID-19 Testing Project (*https://covidtestingproject.org*).

The researchers involved in the project represent **UC Berkeley**, the **University of California San Francisco**, the **Chan**

Zuckerberg Biohub, and the **Innovative Genomics Institute**.

Given the urgent need for comparative data on the assays, the researchers performed head-to-head comparisons of commercially-available lateral flow assays (also known as rapid serology tests) and enzyme-linked immunosorbent assays (ELISAs), the researchers wrote on the web.

"We do not have a gold standard for evaluating serological tests, and that's something we look for in modern medicine," Hsu commented in an interview with THE DARK REPORT. "Therefore," he continued, "we conducted this study by taking in case samples from PCR-positive patients that have been seen in San Francisco hospitals."

Hospital Patients' Specimens

Upon admission, those patients were given the reverse transcription-polymerase chain reaction (RT-PCR) test. Over the course of their hospital stay, blood from these patients was drawn multiple times for follow-up testing and the researchers used those samples in their analysis.

The results of the research could inform healthcare providers and public health and government officials conducting serological testing for the new coronavirus, Hsu explained.

"To power our analysis adequately, we used different time intervals and then placed all the samples into five-day bins," Hsu explained. "This is a question of biology, because we have patients who were seroconverted when their antibodies were expected to rise.

"We know from past research that the IgM antibody is generally thought to rise first, whereas IgG antibodies can take more time while the immune system revs up," noted Hsu. "But without making any assumptions about what type of antibodies would come first and which type of tests might be more sensitive, we wanted to compare all of the assays head-to-head in a very systematic fashion.

"To do that for each of the time-point intervals for every specimen, we tested the performance of each one against the lateral flow assays (LFAs) and against two ELISAs.

LFA versus ELISA Bake-Off

"For each specimen, we wanted to evaluate how the tests performed, collect that data, and then compare the results," he said. "That way we could see what comes from this bake-off.

"Generally what we found is that, at 16 to 20 days, or at more than 20 days, many of these tests were over 80% positive," Hsu explained. "What we don't know, however, is whether that 80% positive rate should be 100% positive. All we know is that these samples were PCR positive before we ran our analysis.

"We don't necessarily know when antibodies will rise and if the antibodies should all have developed to show a rate of 100% positive after three weeks," observed Hsu. "We certainly expect samples from certain patients not to have seroconverted because some might be immunosuppressed, for example. When we reviewed the patient data, we decided that assumption might be correct.

"Also, we had a relatively small sample size of patients who were still hospitalized after 20 days," he recalled. "That makes sense intuitively, because after that many days, these patients would likely have been released because they were from an ambulatory population."

Adding Assays to the Study

During the interview, Hsu said he and his colleagues were considering expanding the sample set beyond the initial 12 COVID-19 serological assays analyzed. At press time, it was not known if the researchers would continue after the FDA issued new rules on May 4. After the initial interview, Hsu did not respond to questions from THE DARK REPORT.

In Manuscript for Peer Review, Researchers Describe Evaluation of COVID-19 Serological Tests

IN A MANUSCRIPT PREPARED LAST MONTH FOR PUBLICATION IN A PEER-REVIEWED JOURNAL, researchers from the COVID-19 Testing Project described the steps they followed to evaluate 12 serological assays.

The researchers collected 130 samples of blood from 80 individuals who had molecular tests that confirmed infections from the SARS-CoV-2 virus. They also had 108 blood samples from another group of patients and those specimens were pre-COVID-19 samples collected from **American Red Cross** blood donors.

The analysis shows that the 12 tests performed relatively well in identifying IgM, IgG, or both antibodies.

"For each test, we quantified detection of IgM and/or IgG antibodies by time period from onset of symptoms and assessed specificity and cross-reactivity," the researchers wrote in the pre-publication manuscript. For their analysis, the researchers tested the patients' specimens over five time periods: one-to-five days, six-to-10 days, 11-to-15 days, 16-to-20 days, and more than 20 days.

"This study also seeks to provide feedback to manufacturers about areas of success and necessary improvement," the researchers explained. That feedback would be useful given that the extent and time to development of antibodies are not fully understood and may vary among all patients, even those who have RT-PCR-confirmed cases, they added.

Rather than report the sensitivity of each assay, the researchers compared the percent positivity rate by time interval, in part because the percent positivity rate rose over time after the onset of symptoms.

One important finding was that high rates of positive results were not reached until at least two weeks after the onset of clinical symptoms. Therefore, "diagnosis at time of symptom onset thus remains dependent on viral detection methods."

Another important result is that for patients with more severe levels of illness, the 12 assays showed a trend to higher positive rates within time intervals. But the researchers urged caution when interpreting this finding because they had limited data from ambulatory patients.

"The majority of samples evaluated after 20 days post-symptom onset had detectable anti-SARS-CoV-2 antibodies, suggesting good to excellent sensitivity for all evaluated tests in hospitalized patients three or more weeks into their disease course," they wrote.

More research is needed on ambulatory or asymptomatic patients to guide the appropriate use of serological testing and it's important to note that researchers do not know the extent to which positive serology-test results reflect a protective immune response, they wrote.

To ensure consistent and meaningful results, Hsu and colleagues recognized that patients tend to respond differently when infected with the virus. Many are asymptomatic initially and may not produce antibodies for many days or several weeks, he said.

"We released our findings as a preprint so that we could report our preliminary results in advance of a formal peer review," he said during the interview on May 2. "We did that because we saw the urgency of the situation and the number of tests that were fraudulent but on the market." If they expand the sample set, the researchers may want to add data from later time points.

Although antibody tests have an important role to play during the pandemic, treating physicians may want to confirm a positive antibody test with another antibody test, he suggested.

"You could confirm results with a different type of serology test that might look at a different antibody isotype or a different type of antigen," Hsu explained. "You could look at IgM verses IgG versus IgA. Or you could look for reactivity against proteins in the virus. That type of confirmatory testing could help improve significantly the specificity of a result by looking across multiple different antigens or antibody isotypes."

From the pre-print manuscript of their findings, the researchers have posted the results of the performance analysis of the 12 assays on the web, and they are interested in adding to the data as they evaluate more tests, Hsu said.

Evaluating More Tests

Some lab companies that make COVID-19 serological tests were interested in adding their tests to the dataset, he said. "There has been an outpouring of interest from many manufacturers or distributors that want their tests evaluated," Hsu commented. "We're trying to figure out the best way to prioritize those requests because there are many more tests that we could evaluate, but we would need more blood samples from infected patients.

"As researchers in this new field, we also want to understand the correspondence between venipuncture serum—which is how our study was conducted—with blood from fingerstick sample collection," commented Hsu. "Plus, we want to increase the number of samples that we have in the later time points from symptom onset.

"Our goal is not to exhaustively evaluate every test—in part because that might not be possible," he added. "And, this work is not what most of us do normally. A lot of the scientists working on this project are repurposing themselves to add to the response among scientists to address this new coronavirus. We want to highlight this issue and perhaps inspire others to scale up this work to do more test-performance evaluations.

Research Highlights about COVID-19 Serology Tests

FOR MOST OF THE TESTS EVALUATED IN THE COVID-19 TESTING PROJECT, the research showed specificity greater than 95% for most of the tests and specificity of more than 99% for two lateral flow assays (LFAs) and for one of the two enzyme-linked immunosorbent assays (ELISAs), the researchers reported.

There were two ELISAs (Epitope and an in-house developed test) and 10 immunochromatographic lateral flow assays:

- **BioMedomics**
- **Bioperfectus**
- **DecomBio**
- **Deep Blue**
- **Innovita**
- **Premier**
- **Sure Check**
- **UCP**
- **VivaDiag**
- **Wondfo**

Researchers provided data on each assay showing the percentage of specificity for each antibody (IgM, IgG, or both) and the percentage of positive results for each antibody at each of the five time intervals (one-to-five days, six-to-10 days, 11-to-15 days, 16-to-20 days, and more than 20 days.

"At the least, we hope that some regulatory bodies will review our data," concluded Hsu. "Those would be very good outcomes for our work."

At a time when large numbers of COVID-19 serological tests are coming into the market, but without the comparable range of data provided with diagnostic assays that are reviewed by the FDA and cleared for use, the work of the COVID-19 Testing Project is a valuable resource for clinical laboratories. TDR

—Joseph Burns

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To Stay Afloat, Dallas AP Group Cut Staff, Payroll

Early planning and federal funding also helped pathologists cut losses from COVID-19 pandemic

CEO SUMMARY: As early cases of COVID-19 spread in some states, pathologists at the 50-member ProPath group in Dallas prepared for a widespread outbreak by preserving cash and working with bankers and other advisors to apply for federal stimulus funding. Executives also furloughed pathologists and other staff temporarily before using federal funds to bring them back. Despite a 65% drop in specimen volume, the executives are confident the pathology group can weather the pandemic.

EARLY IN FEBRUARY, physician-owners at **ProPath** began discussing how to weather the economic effects of the novel coronavirus as the pandemic swept across the country.

Based in Dallas, ProPath is one of the nation's larger physician-owned pathology groups. At the time, there were no reported cases of COVID-19 in Texas and the group's normal specimen volume was unchanged. Still, Cory A. Roberts, MD, the group's President, Chairman, and CEO, and his colleagues became concerned when news reports showed the virus spreading in China, Italy, and other countries, and in New York, Washington State, and elsewhere in the United States.

By the end of February, Roberts informed all staff about the need to prepare for the first confirmed case in Texas of SARS-CoV-2, the virus that causes the illness. "On Feb. 27 I addressed everyone company-wide," Roberts said in an interview with THE DARK REPORT. "I explained all the steps we needed to follow and the importance of ensuring we practiced good hygiene.

"Texas did not get its first case of COVID-19 until about a week later and the Dallas area didn't have its first confirmed cases for another couple of weeks," recalled Roberts. "Our pathology group did not see a drop in specimen volume until the second half of March.

"Rather than waiting for the virus to hit, we anticipated a fall in specimen volume and had to briefly furlough some doctors," he said. A week later, other physicians in the group were furloughed. Furloughing staff was the most difficult step Roberts had to take in response to the pandemic.

Cash-Flow Protection

"Simultaneously, we began aggressive cash-flow protection measures," he added. "We talked to our bankers, outside advisors, outside legal counsel, and our in-house attorney. We gathered information from webinars and conference calls about the pandemic and steps our pathology group should take. Also, our executive team started meeting daily.

"That planning helped us to track the legislation coming out of Congress and to strategize with our bank in advance of the opening of the Paycheck Protection Program (PPP)," Roberts noted. The PPP was built into the Coronavirus Aid, Relief,

and Economic Security Act that Congress passed on March 27.

Chasing Stimulus Funds

"We submitted our PPP loan application on Friday, April 3, the first morning they were accepted," he added. "By about 10 pm we had a loan number and were fully funded late on Wednesday night, April 8. Also, we applied for Medicare Advance payment funds immediately.

"After receiving the PPP funds from the bank, we brought back all our employees and we will be able to keep paying everyone at least through the first week in June," he said. "By that time, we anticipate specimen volume will be approaching normal."

One key to ProPath's success so far was the cash-flow model CFO John Stokes and colleagues designed in March. "The model showed adequate cash on hand through July, even with severe volume drops and no federal relief," he reported. "That gave us confidence that our pathology group was well positioned and would be fine until the work came back and specimen volume picked up."

Conservative Spending Plan

As a large pathology group, developing the financial model in response to the COVID-19 outbreak was a challenge. "We're the largest, 100% physician-owned nationwide pathology practice in the country," Roberts said.

ProPath has an 85,000-square-foot campus on five acres in Dallas that accommodates staff offices and the main corporate lab. The team includes about 50 pathologists and almost 500 employees, including sales and support staff in 10 states. ProPath's pathologists serve as medical directors in 26 Texas hospitals.

In February, ProPath acquired a two-member pathology practice in Fall River, Mass., its only anatomic pathology operation outside of Texas.

During the last two weeks of February and the first week of March, ProPath built its cash-flow model on conservative spending. "Our group halted all travel and capital spending," noted Roberts.

"By early March, we closed the job searches we had for all 22 open positions and began reviewing small-dollar spending," he said. "We then started to hold back on some accounts payable items to conserve cash.

"We were well prepared by the middle of March, and that's before we saw the number of case referrals fall lower and lower as each day passed," Roberts reported.

Volume Dropped in March

"The first week or two that referrals declined occurred during spring break season, which is a big deal here in Texas," he said. "Typically, our group sees a dip in specimen volume during March for that reason. So, it was difficult to separate the true causes. But then, from about March 16 on, our volume started gradually dropping until by the end of the month when we had a significant fall off.

"In fact, by the end of March, incoming case referrals were down to just 30% of normal outpatient biopsy volume," he explained. "Our primary business is outpatient biopsies and testing in addition to inpatient cases.

"Normally, the tissue volume we process in our laboratory averages about 2,400 blocks a day," Roberts added. "But, by the end of March, we were doing only about 600 blocks a day.

"As April ended, our biopsy specimens were down by 65%, compared with the same month last year," said Roberts.

"Our pathology group also does other work, such as flow cytometry, cytogenetics, molecular, and so on," he added. "Molecular testing may be down only about 25% from normal volume.

"All of this other work was impaired less dramatically, and, so far, has remained insulated from the severe drop we saw in biopsies," noted Roberts. "Case referrals were down by 30% for our consulting ser-

While Normal AP Volume Remains Low, Physician Staff Takes on New Responsibilities

ONCE FUNDING ARRIVED LAST MONTH through the federal Paycheck Protection Program (PPP), the 50-member **ProPath** group in Dallas brought back physicians who were furloughed in March.

Because the group's anatomic pathology (AP) specimen volume still remained low due to the virus, the pathologists needed new responsibilities, said Cory A. Roberts, MD, the group's President, Chairman, and CEO. Roberts viewed the unused staff capacity as an opportunity.

"We have an aggressive plan to move ahead on a number of research projects," he said. "Before specimen volume fell sharply at the end of March, these projects were secondary priorities. Now, they have new urgency."

One such priority is to validate a new **Aperio** AT2, the whole-slide imaging (WSI) system that ProPath acquired from **Leica Biosystems** in December. A second is clinical research with academic partners, and a third involves developing artificial intelligence for use in AP.

"Early in the year, we were validating the WSI system because it was a big part of our business plan for 2020," he said. "We expect digital pathology will generate revenue and provide a good return on our investment.

"For example, we expect increased compensation for breast prognostic work using WSI. For that work, there's a higher reimbursement level than with conventional slide review.

"We also are validating that system for primary diagnosis and expect to use digital pathology for a growing portion of our outpatient work—meaning the 2,400 specimen blocks we review each day," Roberts added.

"Using WSI, we can transmit those images to our doctors in other hospitals rather than use couriers."

Accelerated DP Validation

WSI validation ended when pathologists were briefly furloughed in two waves late in March. "As we brought pathologists back, we didn't have clinical work for them. So we developed plans to accelerate the validation," he noted.

"We also accelerated research projects we're doing with academic medical centers," Roberts said. "The pathologists who are not doing clinical work are now writing academic papers full time."

In a separate strategic initiative, ProPath is working with **Reveal Biosciences**, a company in San Diego developing artificial intelligence to increase accuracy and reproducibility for WSI. "We have about 15 projects with Reveal to develop accurate clinical diagnosis tools for artificial intelligence that use their analytic models for anatomic pathology," Roberts said.

vice that includes esoteric testing, such as flow cytometry and bone marrows.

"Another part of our business comes from a consulting service where other pathologists send cases to our subspecialist-pathologists for review," he noted. "That work has remained somewhat insulated too."

ProPath also does testing for women's health. "The volume in women's health is down about 40% to 50% from normal volume," he noted.

Flow Cytometry, IHC

In flow cytometry and immunohistochemistry, the decline in volume is not as deep as it is in biopsies. "Normally, each day we do about 25 specimens in our flow lab," he explained. "The decline in this segment of our business is hard to quan-

tify but the dip was mild, started later, and came back quicker. We also do several hundred immunostains a day for other labs. We send those slides back out to the referring labs. That was another part of our business that was much less affected."

Such a steep decline in specimen volume and case referrals through March and April required furloughing some pathologists and other staff. "As a physician, you never contemplate either furloughing staff or being furloughed," he commented. "So, that decision was a tragic and devastating component of this pandemic.

"Going into the last week of March, as our pathology group saw the crash in volume, a number of fantastic physicians were furloughed on a Sunday night," he continued. "The following week, a few additional physicians were furloughed when it became clear that the number of specimens was still way below normal. At this time, applications for PPP funding were not even open."

Pay Cut for Owners

In addition to conservative spending and staff furloughs, the physician owners agreed to a pay cut. "Owner compensation was cut by 50%, retroactive to March," Roberts reported. "The owners also agreed not to take any pay in April or in the coming months.

"We felt it was important for owners to be the first dollars cut and the last dollars returned," explained Roberts. "Our strategic plan was to act quickly to ensure longevity and hope to return some of those savings to employees after the crisis.

"Also, we made cuts in compensation among salaried team members, specifically to keep as many people on the payroll as possible, even at lower pay rates," he added.

This was happening during the time Congress was developing the trillion-dollar legislation that included the payroll protection program, but before it was signed into law. "Within days of implementing the second round of furloughs, the PPP funding was in our bank account by Thursday, April 9," he reported. "So, we looked at the dollars and the forgiveness factors and decided on Friday, April 10, to bring all employees back under the parameters of the PPP.

Group Is Conserving Cash

"At this moment, financial modeling indicates our pathology group should be good until the first week of June," noted Roberts. "That's when the funds from the PPP end. Our projects indicate our group will have conserved enough cash and the current plan is to keep everyone after that date.

"Even though the group doesn't have enough work to justify retaining that many staff, we're at least able to pay people something," concluded Roberts. "Now, because of our aggressive measures early on, I'm quite hopeful we'll be able to restore people at the end of the PPP period, even if we don't have the income volume of case referrals to match that level of payroll."

Back in February, ProPath's leadership team showed unusual foresight when it recognized that the earliest cases of COVID-19 showing up in Europe and North America could indicate a serious outbreak of the novel coronavirus. That triggered strategic planning and urgent development of a crisis response plan that proved to be prescient.

Global COVID-19 Pandemic

This proactive response to the earliest signs of what quickly evolved into a global pandemic enabled ProPath to quickly identify how the rapid decline in the daily number of incoming case referrals would require immediate action.

Pathologists and pathology practice administrators may want to study the actions ProPath is using to protect the financial position of the group while keeping as many of the pathologists and lab staff on the payroll as possible. TDR

—Joseph Burnsl

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INTELLIGENCE

LATE & LATENT

Items too late to print, too early to report

Clinical laboratories in other countries have similar challenges in responding to the COVID-19 pandemic. In the United Kingdom, the *Independent* reported last week that "Widespread testing for coronavirus has been suspended among staff and patients at hospitals and GP practices serving 3.5 million people because of a shortage of vital chemicals." According to *Independent* reporter Shaun Lintern, medical laboratories serving South London are unable to access adequate supplies of reagents and other clinical lab supplies required to meet the demand for COVID-19 testing.

MORE ON: *COVID-19*

Just as in the United States, the news media in the United Kingdom is publishing stories daily about the gap between the number of COVID-19 tests needed and the ability of medical laboratories in that country to deliver enough COVID-19 tests. The Independent wrote that "the **South West London Pathology Partnership** provides testing for **St. George's Hospital**, **Kingston Hospital Foundation Trust**, **Croydon Health Services Trust**, and **Epsom** and **St. Helier Hospitals Trust**. It also serves more than 200 GPs across the capital."

AUSTRALIAN LABS WANT TO REDUCE DRAW SITE RENTS

In Australia, the COVID-19 pandemic triggered a substantial decline in routine test volumes at the nation's medical laboratories. To cut their costs during the outbreak, several lab companies are asking general practice (GP) clinics to accept a 50% reduction in the rent they pay to maintain blood draw stations in the clinics. However, loss of this revenue is hurting GP practices. *The Guardian* noted that David Dahm, an accounting consultant to GPs in Adelaide, described these GP clinics as "gazing into a 'funding black hole,'" with Dahm adding that "GPs live off [the government's practice incentives program] and pathology rent [for drawing stations in their practices]."

TRANSITIONS

• **Personal Genome Diagnostics** of Baltimore appointed Megan Bailey as its new CEO. Bailey has held executive positions at **Roche Diagnostics** and **Ventana Medical Systems**.

• **Personalis** of San Jose, Calif. announced that Stephen Moore is now its General Counsel. Moore formerly served at **Pacific Biosciences**, **Navigenics**, **Affymetrix**, and **Adobe Systems**.

• Ingo Chakravarty is the new President and CEO of **Mesa Biotech** of San Diego. He previously held positions at **Navican**, **GenMark Diagnostics**, **Gen-Probe**, **Roche Diagnostics**, and **Ventana Medical Systems**.

DARK Daily
Clinical Laboratory and Pathology News/Trends

DARK DAILY UPDATE

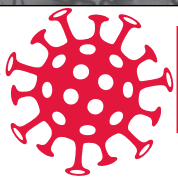
Have you caught the latest e-briefings from DARK Daily? If so, then you'd know about...

...how the **Innovative Genomics Institute** (IGI) at the **Univ. of California, Berkeley** used its research equipment to make a COVID-19 diagnostic testing laboratory operational in just a few weeks. It can do 3,000 tests daily with results in four hours. *You can get the free DARK Daily e-briefings by signing up at www.darkdaily.com.*

That's all the insider intelligence for this report. Look for the next briefing on Monday, June 1, 2020.

Resources and Help for Labs During SARS-CoV-2 Pandemic

Here Now!



COVID-19 STAT INTELLIGENCE BRIEFINGS

A Service of The Dark Intelligence Group

Today, every clinical lab is on the front lines of the SARS-CoV-2 pandemic. Pathologists and lab managers face unprecedented challenges and much uncertainty about the best responses.

Cash flow is dropping. Test mix is changing as routine testing falls off and demand for COVID-19 tests increases. Specimen collection and transport is disrupted.

To help you stay informed and provide you with actionable intelligence, The Dark Report and DarkDaily.com launched the COVID-19 STAT Intelligence Service.

Check **www.covid19briefings.com** to access all features and services.

To share your lab's innovations and successes, contact our Editor at: rmichel@darkreport.com

UPCOMING...

- ***Roche Diagnostics Obtains FDA EUA for Its COVID-19 Serological Test with 99.8% Sensitivity: Is It a Gamechanger?***
- ***First Report on How Medicare and Private Health Insurers Are Reimbursing Claims for Rapid Molecular COVID-19 Claims.***
- ***Effective Ways to Streamline Clinical Lab Operations until Daily Routine Specimen Volumes Return to Pre-pandemic Levels.***

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