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SEPTEMBER 2020 ▪ Vol 52 ▪ No 9

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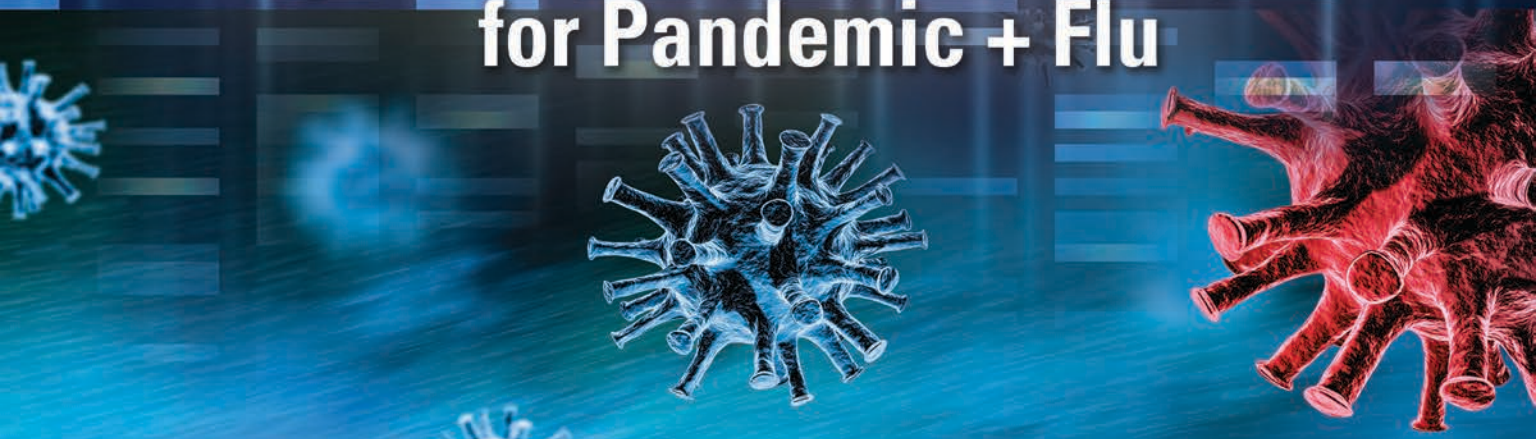
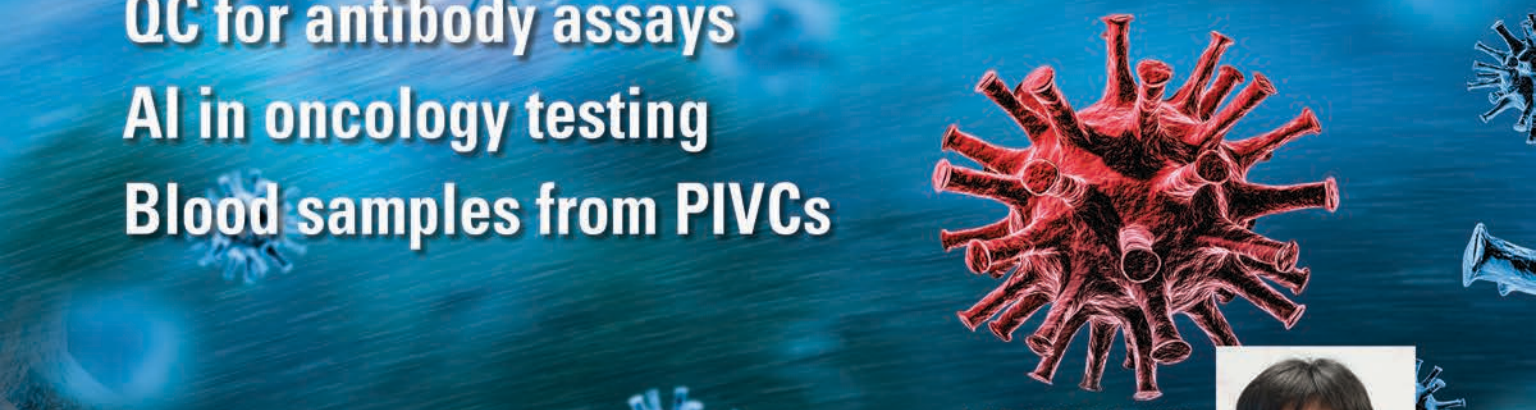


QC for antibody assays

AI in oncology testing

Blood samples from PIVCs



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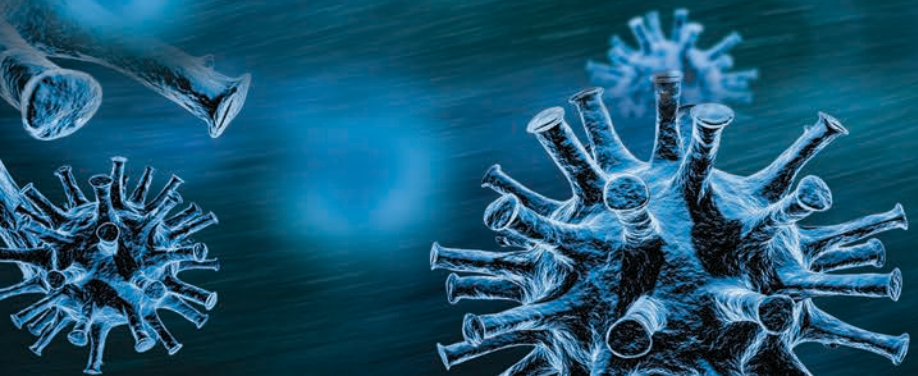

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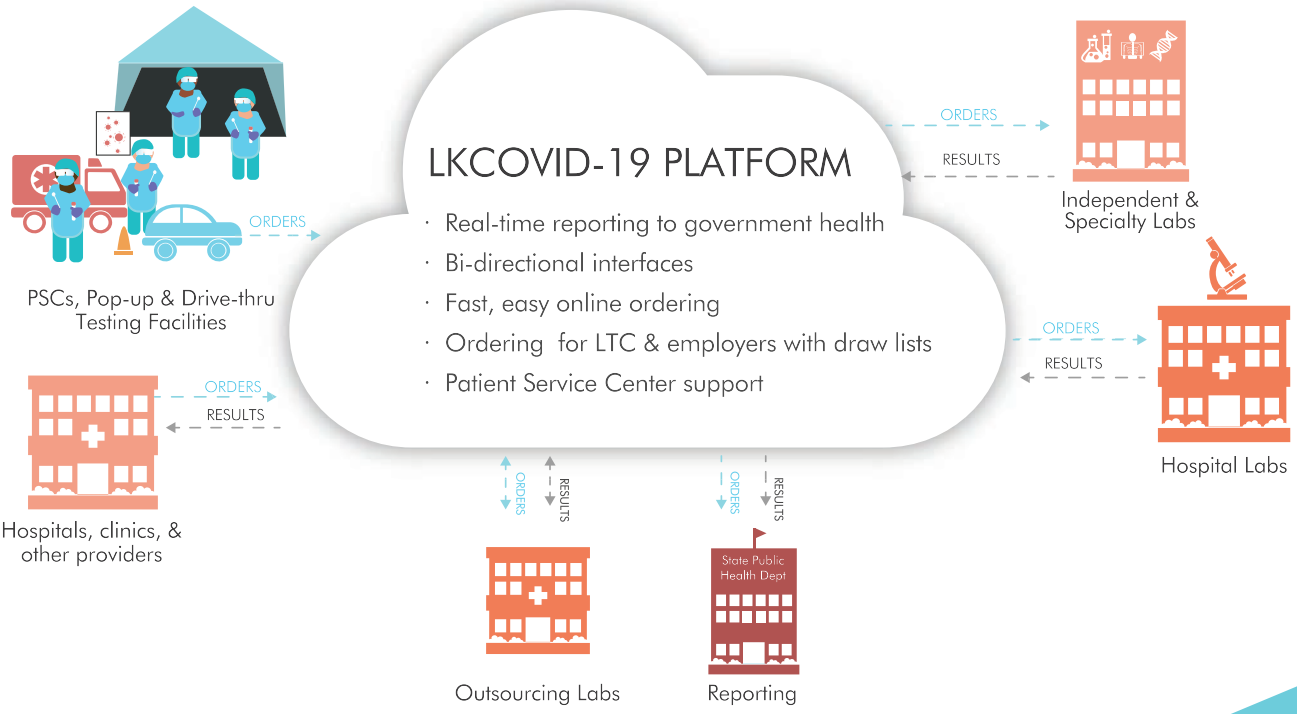

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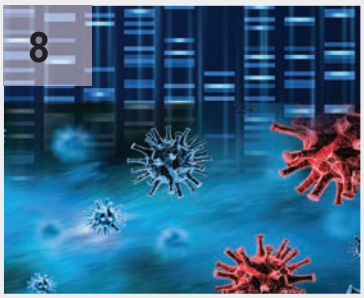

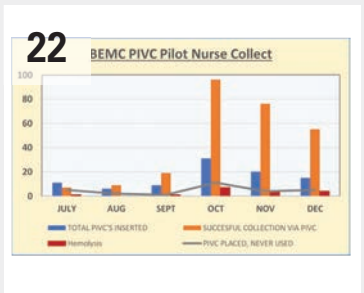

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Laboratory "tools" for job success

By Brenda Silva
Senior Editor

Like any technical job that requires a particular skill set, the level of success is often dependent on having the right tools for the job and knowing how to use them in their intended applications. For members of the clinical laboratory industry, their "tools" include lab equipment, rapid tests and consumables (among others) – all of which require a certain level of training and certification to achieve job success. As part of *Medical Laboratory Observer*'s *(MLO)* recent reader survey, we asked our readers to tell us what they wanted more of in the types of articles and content that matter to them most.

The 30-question reader survey looked for replies to a wide range of questions that included the levels of daily involvement of lab personnel, as well as budget allocation and feedback on whether or not *MLO* provides information on the products and services that are being used every day. And a BIG thank you goes out to our survey respondents, and we say, "We heard you!" – your requests are valued and appreciated, have been taken seriously, and will be evident in upcoming issues of *MLO*.

As reader survey requests and comments were reviewed, our editorial staff included as many topics as possible when drafting our content calendar for 2021. Among the many ways we are planning to get you the information you need to succeed in your jobs is to focus on the topics that many readers said they wanted to learn more about in the future. For example, the topic of certification and testing has shown increased interest since last year's survey, along with the categories of quality control (QC), information technology (IT), rapid and point-of-care (POC) tests, infectious diseases, reagents and lab safety. All of these will be more prevalent in upcoming issues in 2021.

When considering targeted topics for our 2021 calendar, we could not forget to include COVID-19 – the elephant in the lab, if you will. Because of its far-reaching effects and daily global developments, we will continue to include more coverage of the disease in more sections of the magazine.

Due to the concern around COVID-19, and in alignment with the best practices laid out by the Centers for Disease Control and Prevention (CDC), World Health Organization (WHO) and other relevant entities, we also did a survey on the ability or desire of lab directors to travel. As a result, we are launching our Second Annual Lab Directors Summit as a virtual event. Over 92 percent of respondents said they would be interested in a virtual event, and almost the same number said they would not be interested in an in-person event. The upcoming virtual Lab Directors Summit (LDS) is being held October 26-28.

We are planning an exciting and informative program that focuses around you and fellow lab directors, and will allow for the time and **opportunity to get insights on an immediate issue, learn what's working for your peers and what is not, and begin new relationships with colleagues from across the country.**

Keep in mind that as with any position in the clinical lab, acquiring training and accumulating experience remain keys to job success. By way of *MLO*'s reader survey, we were able to learn what's important to you, our readers, and encourage you to contact us with honest, constructive feedback so that we can continue to make *MLO* the go-to magazine for the whole of the clinical lab industry.

I welcome your comments, questions and opinions – please send them to me at bsilva@mlo-online.com.

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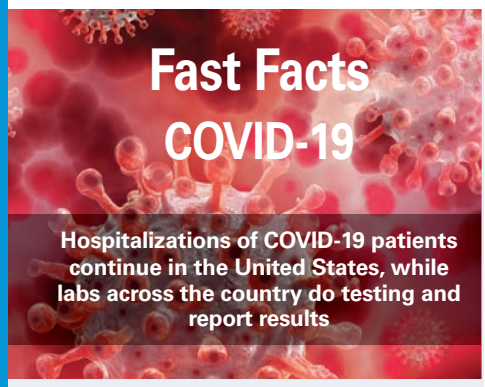

60,062,284*

is the total number of tests

5,403,102*

is the total number of positive tests.

9 percent*

is the percentage of positive tests nationally.

7,492,194*

is the number of tests performed in California, the state with highest number of tests.

94,615*

is the number of tests performed in Wyoming, the state with the fewest tests performed.

$25, 255*

is the average fee-for-service payment per COVID-19 hospitalization.

1-7 days

is the hospital length of stay for 47% of COVID-19 patients in Original Medicare, compared with of a LOS of 8-15 days for 33% of patients, and 16 or more days for 20% of patients.

Sources:
***As of August 3, 2020**
1. https://www.cdc.gov/covid-data-tracker/index.html#testing
2. https://www.cms.gov/files/document/medicare-covid-19-data-snapshot-fact-sheet.pdf

Nearly half of U.S. adults have conditions putting them at risk for severe COVID-19

Nearly half, or 47 percent, of U.S. adults have one of five underlying medical conditions associated with increased risk for severe COVID-19–associated illness, the Centers for Disease Control and Prevention (CDC) reported in its Morbidity and Mortality Weekly Report.

The agency estimated disease risk for 3,142 U.S. counties.

Counties with the highest prevalence were concentrated in the Southeast and Appalachian region. The estimated number of people with these conditions followed population distributions, but the prevalence was higher in more rural counties.

According to numerous previous studies, the risk for severe COVID-19–associated illness (illness requiring hospitalization, admission to an intensive care unit (ICU), mechanical ventilation, or resulting in death) increases with age, as well as the presence of underlying medical conditions, including chronic obstructive pulmonary disease (COPD), cardiovascular disease, diabetes, chronic kidney disease, and obesity, the CDC said.

The overall weighted prevalence of these conditions was 30.9 percent for obesity, 11.4 percent for diabetes, 6.9 percent for COPD, 6.8 percent for heart disease, and 3.1 percent for chronic kidney disease. Counties with the highest prevalence of any condition were concentrated in Southeastern states, particularly in Alabama, Arkansas, Kentucky, Louisiana, Mississippi, Tennessee, and West Virginia, as well as some counties in Oklahoma, South Dakota, Texas, and northern Michigan, among others.

The estimated median prevalence of any condition generally increased as the location became more rural, ranging from 39.4 percent in large central metropolitan counties to 48.8 percent in non-core counties, while the estimated median number of people with any underlying condition ranged from 4,300 in non-core counties to almost 302,000 in large central metropolitan counties.

To reach these findings, the CDC used a small-area estimation approach to determine county-level prevalence of selected conditions associated with severe COVID-19 disease among U.S. adults aged 18 years and older using self-reported data from the 2018 Behavioral Risk Factor Surveillance System (BRFSS), as well as population data from the U.S. Census. Overall, 437,500 people participated in BRFSS, which is a random digit-dialed phone survey.

Antibodies promising in fight against COVID-19

Based on positive results in recent preclinical studies, potently neutralizing antibodies identified by researchers are showing promise as a potential therapy for preventing and treating COVID-19, according to scientists at Vanderbilt University Medical Center (VUMC). The monoclonal antibodies were isolated from the blood of a couple from Wuhan, China, who were diagnosed with COVID-19 after traveling to Toronto, Canada, in late January. They were two of the earliest confirmed cases of COVID-19 in North America.

During the past two years, VUMC researchers led by James Crowe, Jr., MD, and Robert Carnahan, PhD, have developed ultra-fast methods for discovering highly potent antiviral human monoclonal antibodies and validating their ability to protect small animals and non-human primates, all in less than three months.

Reporting in the journal *Nature Medicine*, the researchers and colleagues from across the country describe how they used this rapid antibody discovery platform to isolate hundreds of human monoclonal antibodies against the surface spike (S) protein that enables SARS-CoV-2, the virus that causes COVID-19, to infect lung cells.

In a separate report published in the journal *Nature*, VUMC scientists and their colleagues describe how two of the antibodies, COV2-2196 and COV2-2130, bind to distinct sites on the S protein and either alone or in combination reduce the viral "burden" in infected mice and protect them from weight loss and lung inflammation.

They also found that COV2-2196 and another potent antibody, COV2-2381, given alone protected rhesus macaques from SARS-CoV-2 infection. Collectively these results suggest that these monoclonal antibodies, either alone or in combination, "are promising candidates for prevention or treatment of COVID-19," the researchers concluded.

Drug that calms cytokine storm associated with lower mortality risk among COVID-19 patients

Critically ill COVID-19 patients who received a single dose of a drug that calms an overreacting immune system were 45 percent less likely to die overall, and more likely to be out of the hospital or off a ventilator one month after treatment, compared with those who didn't receive the drug, according to a new study by a team from the University of Michigan.

The lower risk of death in patients who received intravenous tocilizumab happened despite the fact that they also had twice the risk of developing an additional infection, on top of the novel coronavirus. The study is published in *Clinical Infectious Diseases* after being available as a preprint last month.

It suggests a benefit from timely and targeted efforts to calm the "cytokine storm" caused by the immune system's overreaction to the coronavirus. Tocilizumab, originally designed for rheumatoid arthritis (RA), has already been used to calm such storms in patients receiving advanced immunotherapy treatment for cancer.

The researchers base their conclusions on a thorough look back at data from 154 critically ill patients treated at Michigan Medicine, U-M's academic medical center, during the first six weeks of the pandemic's arrival in Michigan from early March to late April. The analysis looked at patients' records through late May.

During that time, when little was known about what would help COVID-19 patients on ventilators, about half of the studied patients received tocilizumab and half did not. Most received it within the 24-hour period surrounding their intubation. This created a natural opportunity for comparing the two groups' outcomes in an observational study, though clinical trials are still needed to truly see if the drug provides a benefit, the authors say.

Simple blood test can predict severity of COVID-19 for some patients

An early prognosis factor that could be a key to determining who will suffer greater effects from COVID-19, and help clinicians better prepare for these patients, may have been uncovered by researchers at The University of Texas Health Science Center at Houston (UTHealth). Results of the findings were published in the *International Journal of Laboratory Hematology.*

The severity of COVID-19 infections can range from little or no symptoms for some patients to fighting for their lives in the intensive care unit (ICU) for others. Little is known about what causes these differences.

"Because of the uncertainty surrounding the implications of this virus, we knew there needed to be a prognostic factor that could aid hospital workers in managing COVID-19," said Ahmad Farooq, MD, corresponding author on the study, and assistant professor of gastroenterology at McGovern Medical School at UTHealth. "In this study, we discovered evidence of a relationship between lymphocytopenia and disease severity that could really help clinicians prepare for critically ill patients."

Lymphocytopenia is the condition of having an abnormally low levels of white blood cells, called lymphocytes, which are key components of the immune system. Using a cohort of 57 patients from a local Houston hospital, researchers analyzed basic, clinical, and laboratory data from a simple blood draw and found that patients who were admitted into an ICU showed signs of lymphocytopenia compared to patients who were not in the ICU.

At the time of hospital admission, patients who ended up in the ICU had lymphocytopenia in comparison to those not needing ICU admission, revealing that blood lymphocyte count could be a predictive marker in identifying who may be admitted into the ICU and suffer severe implications. Additionally, researchers found that patients with lymphocytopenia were more likely to develop an acute kidney injury (AKI) during admission. According to Farooq, mortality rates are higher in patients who have both COVID-19 and AKI compared to those without AKI.

Antibodies against SARS-CoV-2 may diminish over time in mild cases of infection

A study by UCLA researchers shows that in people with mild cases of COVID-19, antibodies against SARS-CoV-2 — the virus that causes the disease — drop sharply over the first three months after infection, decreasing by roughly half every 36 days. If sustained at that rate, the antibodies would disappear within about a year, according to a news release from UCLA.

Previous reports have suggested that antibodies against the novel coronavirus are short-lived, but the rate at which they decrease has not been carefully defined.

The researchers studied 20 women and 14 men who recovered from mild cases of COVID-19. Antibody tests were conducted at an average of 36 days and 82 days after the initial symptoms of infection.

The findings raise concerns about antibody-based "immunity passports," the potential for herd immunity and the reliability of antibody tests for estimating past infections. In addition, the findings may have implications for the durability of antibody-based vaccines.

Genetic factors may influence COVID-19 susceptibility

A new Cleveland Clinic study has identified genetic factors that may influence susceptibility to COVID-19, which could guide personalized treatment. In this study, a team of researchers led by Feixiong Cheng, PhD, Genomic Medicine Institute, investigated genetic susceptibility to COVID-19 by examining DNA polymorphisms (variations in DNA sequences) in the ACE2 and TMPRSS2 genes. ACE2 and TMPRSS2 produce enzymes (ACE2 and TMPRSS2, respectively) that enable the virus to enter and infect human cells.

Looking at 81,000 human genomes from three genomic databases, they found 437 non-synonymous single-nucleotide variants in the protein-coding regions of ACE2 and TMPRSS2. They identified multiple potentially deleterious polymorphisms in both genes (63 in ACE2; 68 in TMPRSS2) that offer potential explanations for different genetic susceptibility to COVID-19, as well as for risk factors.

Several ACE2 variants were found to be associated with cardiovascular and pulmonary conditions by potentially altering the angiotensinogen-ACE2 interaction. In addition, germline deleterious variants in the coding region of TMPRSS2, a key gene in prostate cancer, were found to occur in different cancer types, suggesting that oncogenic roles of TMPRSS2 may be linked to poor outcomes with COVID-19.

These findings demonstrate a possible association between ACE2 and TMPRSS2 polymorphisms and COVID-19 susceptibility and indicate that a systematic investigation of the functional polymorphisms in ACE2 and TMPRSS2 among different populations could pave the way for precision medicine and personalized treatment strategies for COVID-19. However, all investigations in this study were performed in general populations, not with COVID-19 patient genetic data.

"Because we currently have no approved drugs for COVID-19, repurposing already approved drugs could be an efficient and cost-effective approach to developing prevention and treatment strategies," Dr. Cheng said. "The more we know about the genetic factors influencing COVID-19 susceptibility, the better we will be able to determine the clinical efficacy of potential treatments."

As the pandemic meets flu season, labs turn to rapid molecular testing

By Sherry Dunbar, MBA, PhD

The upcoming 2020-2021 flu season promises to bring new challenges for diagnosing and treating patients. While flu season is predictably unpredictable, never before have we faced its onset while simultaneously fighting a non-flu respiratory pandemic. Problems typically encountered during flu season are likely to be compounded by the COVID-19 landscape.

The challenges of respiratory testing during flu season are well known. Influenza causes many symptoms shared with other respiratory infections – and indeed even with some other respiratory conditions not associated with pathogens – making it difficult to diagnose. Answers are needed quickly, but historically, rapid tests, such as immunoassays for viral antigens, were far less accurate than conventional laboratory tests. A broad range of molecular test options, from flu-only tests to broad panels of respiratory pathogens, has been helpful for the laboratory but can be confusing for physicians to navigate. The right test for one patient can be entirely wrong for the next patient. For lab managers, knowing how many tests, reagents, and other supplies to stock in preparation for getting through flu season can be difficult as well.

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LEARNING OBJECTIVES

Upon completion of this article, the reader will be able to:

1. Describe technical and-non-technical challenges labs face in diagnosing patients during a season marked by both flu and COVID-19.
2. Describe the advantages and disadvantages of different types of assays for diagnosing respiratory diseases such as flu and COVID-19.
3. Recall the Infectious Disease Society of America's (IDSA) recommendations on the preferred assays for diagnosing flu.
4. Describe how combination molecular assays can be used to detect the presence of multiple respiratory diseases from a single specimen.

And those are just the expected hurdles in a regular flu season. This fall and winter, physicians and clinical lab professionals will have to add the new variable of COVID-19. At a minimum, the pandemic means that clinical labs will not be able to rely solely on tried-and-true flu tests. Depending on local prevalence of COVID-19 infections, each lab will have to determine whether to add SARS-CoV-2 testing for all patients with respiratory symptoms, or whether they will need an algorithm to select which patients get tested for both flu and COVID-19.

As of July, the U.S. Food and Drug Administration (FDA) had already granted emergency use authorization (EUA) for three combination tests for flu and SARS-CoV-2, including one developed by the Centers for Disease Control and Prevention (CDC).[1] Other diagnostic manufacturers will likely make similar tests available. While this will be good for patients and healthcare providers, it places the burden of validating new assays on clinical lab teams already stretched thin by the pandemic.

Respiratory testing challenges

Diagnosing patients with non-specific respiratory symptoms during flu season has evolved in recent years. The base challenges have not changed: multiple strains of flu, season-to-season variability of virulence and severity, the broad range of possible pathogens, and scaling to meet unexpected surges in testing demand.

However, the choice of test has changed. With the major push to slow the spread of antimicrobial resistance by reducing the unnecessary use of antibiotics, physicians can no longer wait a few days to get test results for possible flu cases. There is now significant pressure to deploy assays that generate rapid results.

Unfortunately, some tests have enabled fast results at the cost of accuracy. Rapid antigen flu tests have been widely adopted in recent years, particularly in doctors' offices and other outpatient environments where getting results in 15 minutes represented a huge advance for patient care. But numerous studies have shown that rapid antigen tests tend to have low sensitivity, leading to a high number of false negative results.

New guidelines for influenza testing issued by the Infectious Diseases Society of America (IDSA) last year recommend against the use of rapid antigen tests. A broad survey of many studies found "pooled sensitivities of 54 percent and 53 percent to detect influenza A and

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influenza B virus antigens, respectively," according to the new guidelines.[2]

The IDSA now recommends the use of rapid molecular tests, particularly those based on reverse-transcription polymerase chain reaction (RT-PCR). While these are typically not as fast as the 15-minute rapid antigen tests, they often produce results in just a few hours, which still allows healthcare providers to deliver same-day answers to patients along with guidance for the most appropriate treatment, if any. According to the IDSA, rapid molecular diagnostics are now preferred over viral culture, immunofluorescence tests, serologic testing, and, of course, rapid antigen tests.

Confounded by COVID-19

Clinical lab professionals have never experienced the vagaries of flu season while also battling a worldwide, non-flu respiratory pandemic. It remains to be seen exactly how the COVID-19 situation will compound the challenges of respiratory testing, but we can make some educated guesses.

It is possible that the 2020-2021 flu season could be significantly alleviated by measures many people are already taking to avoid being infected by SARS-CoV-2, such as mask wearing and social distancing. These are the same measures recommended for reducing the spread of influenza, though in the United States most people do not dramatically alter their behavior to avoid the flu.

Similarly, if the substantial reduction in domestic and international travel seen so far in 2020 continues into flu season, this could also limit the spread of influenza. Even if some travel resumes, restrictions that prevent people from certain countries from entering other countries or regions could have the secondary benefit of leading to a milder flu season.

Those are the potential upsides of COVID-19 on the flu landscape. Among clinical laboratories, there is far more focus on the possible downsides.

The SARS-CoV-2 testing fiasco that played out in the United States, as the pandemic reached this country, has not yet been overcome. Capacity limits have in many cases prevented labs from reporting results in a timely manner, even when the tests they use take just hours to generate data.[3] Supply chain problems have made some test reagents and equipment difficult to stock.[4] These challenges may well follow us into flu season and could make it harder for labs to manage even low levels of influenza testing.

Because the symptoms of COVID-19 are maddeningly non-specific, labs will likely have to run flu and SARS-CoV-2 tests for each patient suspected of having a respiratory infection, or they will have to validate and implement new tests that encompass those viruses, as well as respiratory syncytial virus (RSV), another common culprit in respiratory infections.

Finally, we must anticipate the confounding variable of co-infections. Studies published from earlier in the pandemic, which reviewed data from the tail end of the previous flu season, found that influenza A and RSV were the most common viruses seen in COVID-19 patients with co-infections.[5,6] Currently there is insufficient data to determine the effect of such co-infections on clinical outcomes, but it is possible that the severity of a SARS-CoV-2 infection is altered by the presence of other pathogens. Therefore, it will be important for clinical laboratories to have the necessary tools to detect cases of co-infection as flu season ramps up.

Using molecular diagnostics

Molecular tests, such as RT-PCR tests recommended by the IDSA for flu testing, have a number of features that make them a good fit for the challenges of this upcoming flu season. They have higher sensitivity than rapid antigen tests or even the previous gold standard, conventional direct or indirect fluorescent antibody (DFA or IFA) assays.[7,8] This accuracy will be more important than ever as clinical lab professionals confront a potentially high prevalence of both SARS-CoV-2 and influenza at the same time in the patient populations they serve.

Table 1: IDSA List of influenza diagnostic assays

Assay type	Turnaround Time	Performance
Rapid molecular assay	15-30 minutes	High sensitivity; high specificity
Rapid influenza diagnostic test	10–15 minutes	Low to moderate sensitivity (higher with analyzer device); high specificity
Direct and indirect		
Immunofluorescence assays	1-4 hours	Moderate sensitivity; high specificity
Multiplex molecular assays	1-2 hours	High sensitivity; high specificity
Molecular assays (including RT-PCR)	1-8 hours	High sensitivity; high specificity
Viral culture	3-10 days	High sensitivity; high specificity

Source: Infectious Diseases Society of America (see reference #2)

Table 2: Co-infections with SARS-CoV-2 (Listed in order of prevalence)

Respiratory syncytial virus
Influenza A
Rhino/enteroviruses
Influenza B
Parainfluenzae
Other coronaviridae
Adenovirus
Human metapneumovirus
Epstein-Barr virus
Coxsackievirus
Cytomegalovirus

Source: Journal of Infection (See reference #6)

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With many options to choose from, molecular assays also tend to be amenable to tailoring for specific needs of various patient demographics. Molecular tests can be used to detect a single pathogen (e.g., SARS-CoV-2), a few related pathogens (e.g., influenza A and B), a handful of common pathogens that cause similar symptoms (e.g., influenza A/B and RSV), or the majority of organisms commonly associated with respiratory symptoms (including viral and bacterial pathogens). During a typical flu season, an otherwise healthy patient would likely need to just test for flu A/B and RSV. Meanwhile, an immunocompromised patient admitted to the hospital could be tested with a broad panel of respiratory pathogens, as the IDSA flu guidelines recommend.

In the COVID-19 era, this flexibility will also be important, but this time the SARS-CoV-2 virus must be factored in. A mini panel test including flu A/B, RSV, and SARS-CoV-2 will be an important tool to help lab staff quickly test for the most common respiratory pathogens without over-testing, giving them the ability to detect common viral co-infections from a single assay. The recently released CDC test, covering SARS-CoV-2 and flu A/B, could be an important tool for clinical labs this fall and winter.[9] Numerous other respiratory assays incorporating COVID-19 are likely to be available as well.

Another key feature of molecular diagnostics is their ease of use. While the first wave of molecular tests was reserved for use in high-complexity laboratories, more recent molecular platforms have been streamlined to allow their use in labs of moderate complexity or the CLIA-waived setting. Today, there are a number of sample-to-answer platforms that rely on automation to limit the hands-on time needed from lab technicians. Some tests are as straightforward as loading samples into a cartridge or cassette, insertion into an automated instrument, and pressing the "start" button. In addition to easing the burden on medical technologists, these kinds of platforms also make it easier for labs to scale capacity to meet surges in demand, without requiring extra staffing resources.

These automated platforms can also provide rapid turnaround times. Some instruments require as little as 20 minutes to report results, and many others take just a few hours. This gives clinical labs many options for respiratory testing, while facilitating same-day reporting of results back to physicians and patients for optimal treatment or isolation protocols.

Last but not least, the multiplexing capability of molecular tests – that is, the ability to detect more than one pathogen from a single assay – should ease the pressure on the supply chain. Having to test for COVID-19 and flu separately requires two nasal swabs, two test kits, and twice as many reagents. By multiplexing these in a single test, lab staff will be able to conserve precious resources and samples and test more patients without running out of supplies.

Other factors

Beyond the technical specifications of respiratory testing for the upcoming flu season, several other factors should be taken into account to plan for a reliable and efficient testing strategy. Exactly how these elements will shape respiratory testing remains unclear, but they are important to consider. Taken as a whole, though, they argue for as much flexibility as possible in clinical laboratory testing strategies.

Reimbursement is always a testing concern, and the addition of COVID-19 in flu season could increase the complexity of managing costs for labs and patients. Both public and private payers have strongly preferred targeted testing to broad panel testing in many situations.[10] With the urgency of the COVID-19 pandemic, it is reasonable to hope that insurers will consider a panel covering at least flu and SARS-CoV-2 as the most responsible approach and reimburse accordingly. But as of this summer, these important determinations had not been made. Lab managers may have to plan for a targeted panel test but have a backup plan available for reimbursable single-pathogen tests for certain groups of patients if needed.

Predicting flu testing volume may also be more difficult than usual this year. In addition to the usual unknowns related to how effective the new flu vaccine will be (it typically falls between 20 percent and 60 percent), there is the additional complexity of estimating how many people will get the vaccine.[11] While the ongoing pandemic may motivate more people to get vaccinated due to their increased fears of getting sick, it may also depress vaccination rates if people are too afraid of getting COVID-19 to go to the doctor's office or the pharmacy for a flu shot. This will

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Molecular tests can be used to detect a single pathogen or multiple pathogens that cause similar symptoms.

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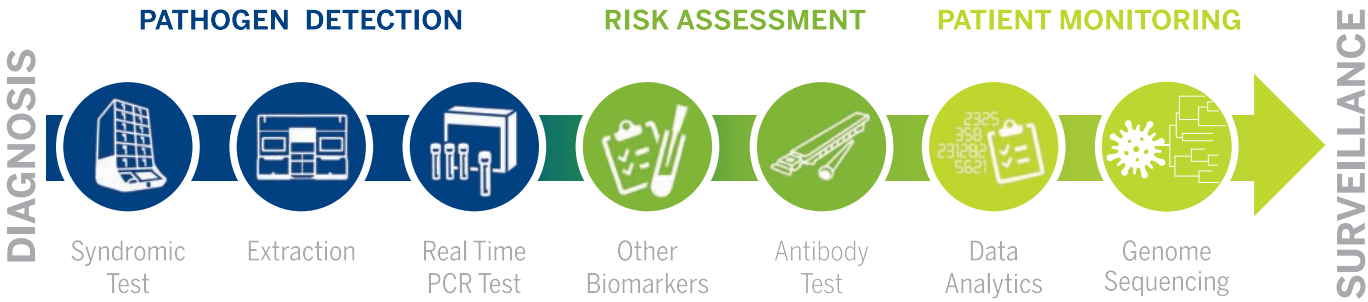

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put extra pressure on clinical labs to plan for testing capacity, which may be much lower than usual, much higher than usual, or anywhere in between. Having automated molecular diagnostic platforms that can handle stat or batch testing with minimal hands-on time will help laboratory teams deal with unexpected peaks in demand.

Another factor with unknown consequences is the adoption of pooled testing as a strategy to increase capacity for detecting SARS-CoV-2. The purpose of pooled testing is to alleviate the strain on testing resources and reduce the number of tests required by combining samples in a single diagnostic run. The strategy only works, though, if COVID-19 prevalence in a community remains low. In that case, the majority of tests will come back negative and no further testing needs to be done. But if the positivity rate rises, more pooled samples will test positive, which will require further testing of each individual sample and not lead to a net decrease in the total tests required. The test used would also have to be exquisitely sensitive to be able to detect a positive that has been diluted by other samples, or there would have to be a concentration step prior to processing. If sample pooling becomes widely used, it could reduce demand for combined SARS-CoV-2/flu tests during flu season, at least in regions where the prevalence of COVID-19 infections remains low.

Courtesy of Luminex

The addition of COVID-19 during flu season could increase the complexity of managing testing costs.

In Review

Bracing for flu season is challenging for most clinical labs even in the best of times. With the COVID-19 pandemic, though, laboratories will face an unprecedented respiratory testing situation this fall and winter. Rapid molecular tests and flexible platforms that allow for multiplexing several pathogens in a single assay will be an essential tool for dealing with the potential crisis that lies ahead of us and should help to ease the supply chain stress associated with dramatically higher testing rates.

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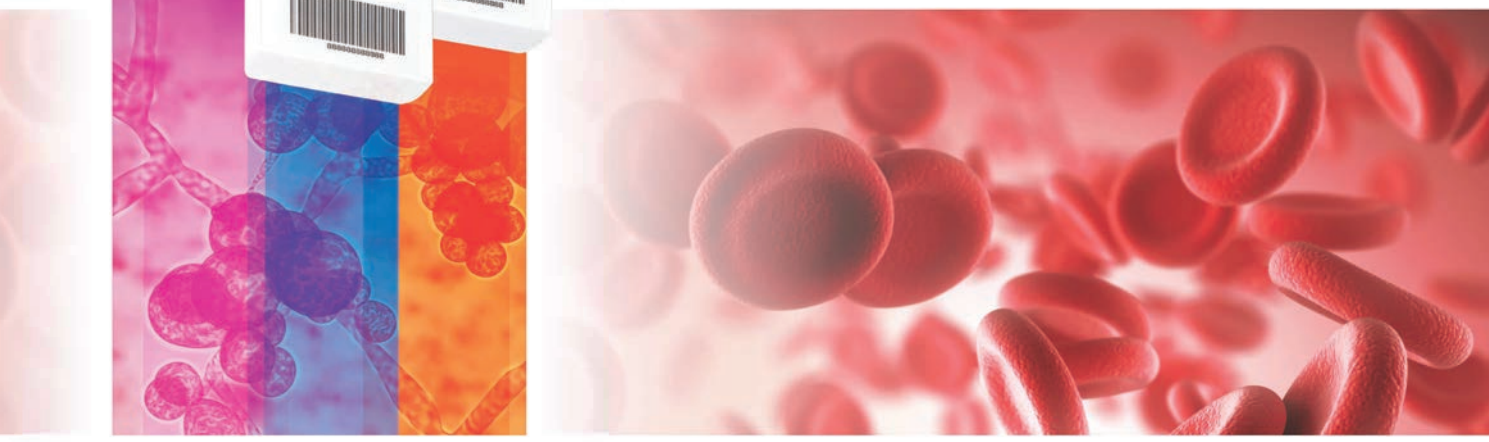

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1. Rapid tests, such as immunoassays for viral antigens, were _____ conventional laboratory tests.
- A. far less accurate than
- B. far more accurate than
- C. as accurate as
- D. slightly less accurate than

2. A broad range of molecular test options, from flu-only tests to broad panels of respiratory pathogens, has been helpful for the laboratory but can be____ for physicians to navigate.
- A. simple
- B. confusing
- C. intuitive
- D. challenging

3. As of July, the U.S. Food and Drug Administration (FDA) had already granted emergency use authorization for _____ combination tests for flu and SARS-CoV-2.
- A. one
- B. two
- C. three
- D. five

4. With the major push to slow the spread of antimicrobial resistance by reducing the unnecessary use of antibiotics, physicians can no longer wait a few days to get test results for possible flu cases.
- A. true
- B. false

5. But numerous studies have shown that rapid antigen tests tend to have____, leading to a high number of ____results.
- A. high sensitivity; false positive
- B. low sensitivity; false negative
- C. low sensitivity; false positive
- D. high sensitivity; false negative

6. New guidelines for influenza testing issued by the Infectious Diseases Society of America (IDSA) last year recommend against the use of ____ tests.
- A. rapid antigen
- B. serology
- C. RT-PCR
- D. viral culture

7. The IDSA now recommends the use of _____.
- A. rapid molecular tests
- B. direct and indirect immunofluorescence assays
- C. rapid cell culture
- D. molecular assays

8. ____ and _____ were the most common viruses seen in COVID-19 patients with co-infections.
- A. influenza A; Influenza B
- B. influenza B; RSV
- C. parainfluenzae; influenza B
- D. influenza A; RSV

9. Currently there is insufficient data to determine the effect of such co-infections on clinical outcomes, but it is possible that the severity of a SARS-CoV-2 infection is altered by the presence of _____.
- A. other pathogens
- B. co-morbidities
- C. environmental allergies
- D. the common cold

10. Molecular tests have higher sensitivity than rapid antigen tests or even the previous gold standard, ____.
- A. conventional direct or indirect fluorescent antibody (DFA or IFA) assays
- B. serology tests
- C. viral cultures
- D. rapid influenza diagnostic tests

11. An immunocompromised patient admitted to the hospital could be tested with a broad panel of respiratory pathogens, as the IDSA flu guidelines recommend.
- A. true
- B. false

12. A mini panel test including flu A/B, ____ and SARS-CoV-2 will be an important tool to help lab staff quickly test for the most common respiratory pathogens without over-testing.
- A. Epstein-Barr virus
- B. RSV
- C. Parainfluenzae
- D. Adenovirus

13. Today, there are a number of sample-to-answer platforms that rely on _____to limit the hands-on time needed from lab technicians.
- A. integration with a laboratory information system
- B. test kits
- C. automation
- D. reagents

14. In addition to easing the burden on medical technologists, these kinds of platforms also make it easier for labs to _____ to meet surges in demand, without requiring extra _____.
- A. scale capacity; test kits
- B. add staffing resources; test kits
- C. add staffing resources; reagents
- D. scale capacity; staffing resources

15. Some automated testing instruments require as little as _____ minutes to report results, and many others take just a few hours.
- A. 10
- B. 20
- C. 30
- D. 40

16. _____ is always a testing concern, and the addition of COVID-19 in flu season could increase the complexity of managing costs for labs and patients.
- A. sourcing supplies
- B. reimbursement
- C. staffing
- D. reducing complexity

17. With the urgency of the COVID-19 pandemic, it is reasonable to hope that insurers will consider a panel covering at least flu and SARS-CoV-2 and RSV as the most responsible approach and reimburse accordingly.
- A. true
- B. false

18. In addition to the usual unknowns related to how effective the new flu vaccine will be (it typically falls between ___percent and ___ percent), there is the additional complexity of estimating how many people will get the vaccine.
- A. 20; 60
- B. 30; 50
- C. 40; 50
- D. 20; 50

19. The pooled-testing strategy only works, though, if COVID-19 prevalence in a community remains _____.
- A. high
- B. static
- C. low
- D. moderate

20. _____ tests and flexible platforms that allow for multiplexing several pathogens in a single assay will be an essential tool for dealing with the potential crisis that lies ahead of us and should help to ease the _____stress associated with dramatically higher testing rates.
- A. rapid molecular; reimbursement
- B. rapid molecular; supply chain
- C. antigen; staffing
- D. antigen; supply chain

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Diagnostic accuracy and reliability remain key in SARS-CoV-2 testing

By Emma Callaghan

The SARS-CoV-2 strain of coronavirus, which leads to the disease COVID-19, presents in many as a minor cold or flu; however, for those with health complications, including autoimmune diseases, asthma, heart disease and diabetes, the risk of developing serious illness and adverse outcomes is much greater.

Currently, it is estimated that as many as 1 in 6 will experience complications that could be life-threatening.[1] Because of the spread and devastation of COVID-19, laboratory diagnostics plays an even more essential role in the diagnosis and management of suspected cases or affected patients. As in the past, clinicians are looking to accurate and reliable controls and reagents to provide the most efficacy in results.

As the spread and devastation of the COVID-19 pandemic continues to grow, it is vital that fast and accurate diagnostic testing strategies are implemented for effective risk stratification, monitoring of treatment and recovery.

Cytokine storms

A cytokine storm, a hyperactive immune response, is a grave complication associated with SARS-CoV-2, triggering life-threatening pneumonia, acute respiratory distress syndrome (ARDS) and multiple organ failure.[2, 3] Early detection of such inflammatory markers can indicate the presence of a cytokine storm and allow timely therapeutic intervention.[4]

It is estimated that cytokine storms occur in up to 5 percent of severe COVID-19 cases, with high levels of several inflammatory cytokines including IL-6, IL-8, IL-10, and TNF-alpha identified. Due to the elevation of several pro-inflammatory and anti-inflammatory cytokines, a multiplex immunoassay approach can offer several advantages over the widely utilized single ELISA tests. The simultaneous detection of multiple cytokines from a single patient sample will provide clinicians with a detailed picture and complete patient profile, facilitating a personalized medicine approach.[5, 6]

Renal function

The National Institute for Health and Care Excellence (NICE) recommends all COVID-19 patients are assessed for Acute Kidney Injury (AKI) on admission to a hospital and their condition monitored throughout their stay. AKI is a common complication of COVID-19, especially in diabetic patients.[7]

Serum creatinine (SCr) is the commonly utilized screening test for renal impairment; however, it is important to consider the accuracy and reliability of the method. The Jaffe and enzymatic methods are the readily available methods of SCr determination; and while the Jaffe method is less expensive, it is more susceptible to interferences. These interferences can lead to the misdiagnosis of patients, which isn't ideal in the current pandemic.[7] Moreover, the sensitivity of SCr in the early detection of renal disease is poor, as SCr is insensitive to small changes in glomerular filtration rate (GFR), with up to 50 percent of renal function potentially lost before significant SCr levels become detectable.[8, 9] Cystatin C (CysC) is a superior marker of renal function and has been identified to be useful in the determination of the extent of renal damage, as well as distinguishing those with severe and mild COVID-19.[10]

Although CysC C is a superior marker of renal impairment, employing a multi-marker approach could identify renal disease or injury at a much earlier stage. Using current technologies, renal disease is typically diagnosed at around stage 4 or 5 when moderate to severe damage has already occurred. Using a multiplex approach, damage can be identified much earlier and in many cases before symptoms arise.

Hepatic function

Patients with abnormal liver function tests are at a significantly higher risk of developing severe disease, and complications such as pneumonia.[11] Significantly elevated bilirubin levels, three times the upper limit, have been observed in COVID-19 patients.[11, 12]

The diazo method is commonly utilized in bilirubin testing; however, superior methods exist. The vanadate oxidation (VO) method has many advantages particularly in hemolytic and lipemic samples. These advantages are particularly evident in neonatal and infant populations where hemolysis is extremely common. Moreover, the VO method offers a wider analytical measurement range.[13]

Other liver function markers are known to be elevated in COVID-19 patients including both AST and ALT, with markers like albumin decreased.

The importance of Lp(a) testing

Lipoprotein(a) / Lp(a) is a strong independent marker of coronary heart disease risk in patients with heterozygous familial hypercholesterolemia (HeFH) and has recently been identified as a key risk marker of cardiovascular complications in COVID-19 patients. Those with either baseline elevated Lp(a) or those whose Lp(a) levels increased following infection from COVID-19, or both, may be at a significantly increased risk of developing thromboses. Consideration should be given to measurement of Lp(a) and prophylactic anticoagulation of infected patients to reduce the risk. Elevated Lp(a) levels may also cause acute destabilization of pre-existing but quiescent, atherosclerotic plaques, which could induce an acute myocardial infarction or stroke.[14]

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The biggest challenge that exists surrounding Lp(a) measurement is the heterogeneity of the apo(a) isoforms, resulting in the underestimation or overestimation of Lp(a) concentrations. In immunoassays, the variable numbers of repeated KIV-2 units in Lp(a) act as multiple epitopes. This is where standardization across calibrators is vital. Unless the calibrants do have the same range of isoforms as test samples, those with higher numbers of the KIV-2 repeat will represent with an overestimation in Lp(a) concentrations, while those with smaller numbers of the KIV-2 repeat will represent with an underestimation. The smaller isoforms are strongly associated with higher Lp(a) concentrations.[15]

The gold standard Lp(a) method is the Northwest Lipid Metabolism and Diabetes Research Laboratory (NLMDRKL) method, which employs an isoform insensitive antibody and is meticulously calibrated with well-characterized material; however, this test is not commercially available.[15]

With Lp(a) assays that are standardized to the WHO/IFCC (World Health Organization/International Federation of Clinical Chemistry) reference material, transferring values from mg/dl to nmol/l are more uniform. The assay considered the most reliable commercially available Lp(a) assay is so because:[15]

1. The isoform size variations are reduced as a range of calibrators from separate pools of serum used, which covered a range of Lp(a) concentrations.
2. The isoform size and concentrations are inversely correlated – better matching calibrants with test samples.
3. Methods are calibrated in nmol/l and traceable to WHO/IFCC reference material and give acceptable bias compared with the NLMDRL gold standard method.

Arguably as important as laboratory testing is the issue of internal and external quality control (QC). The accuracy and reliability of lab data and test results are looked to as the basis for most medical decisions. As such, it is even more imperative that the controls used in lab tests are of the highest quality.

Importance of internal QC

Seventy percent of medical decisions are based on laboratory data. Consequently, it is imperative that the information generated by the laboratory is accurate, timely and readily understandable by the end user. Quality control (QC) is run alongside the patient sample to determine the validity of the assay in accordance with the specifications.[16] Consequently, QC ensures both accuracy and precision of patient sample results. QC should be designed to be commutable, so that the controls react to the test system in the same manner as the patient sample, which aids laboratories in meeting the ISO 15189:2012 requirement and ultimately ensures accurate and reliable instrument performance.[17]

ISO 15189:2012 states: *"The laboratory should choose concentrations of control materials, wherever possible especially at or near clinical decisions values, which ensure the validity of decisions made."* Furthermore, ISO 15189:2012 also states: *"Use of independent third-party control materials should be considered, either instead of, or in addition to, any control materials supplied by the reagent or instrument manufacturer."*

These requirements highlight that third-party controls should be employed to challenge laboratory instruments throughout the patient reportable range. The presence of analytes at clinically relevant decision levels not only aid in ensuring accurate instrument performance but maximize laboratory efficiency through the elimination of additional low/high concentration controls, an unnecessary additional expense.[18]

During the SARS-CoV-2 pandemic, it is vital that laboratories are adhering to and meeting the ISO 15189:2012 requirement to ensure accurate and reliable test results for COVID-19 adverse outcomes for swift and effective treatment plan implementation. In turn, this will ensure increasing confidence that performance mirrors that of the patient sample, producing accurate and reliable results, enabling effective treatment plan intervention.

Importance of external QC

External quality assessment (EQA) is a critical aspect of the laboratory quality management system. EQA is a method that enables a laboratory to compare their testing with another laboratory. The ISO/IEC Guide 43-1: 1997 states: *"Proficiency testing schemes (PTS) are interlaboratory comparisons that are organized regularly to assess the performance of analytical laboratories and the competence of the analytical personnel."* EQA participation is essential for laboratories that are accredited, or plan to seek accreditation.[19]

ISO 15189:2012 addresses EQA requirements for laboratories, highlighting the necessity for a laboratory to participate in interlaboratory comparisons.[19] Selecting an EQA provider who is accredited to ISO/IEC 17043:2010 is ideal as it guarantees high quality programs that are fit for purpose and assists laboratories in achieving their own accreditation.[20]

During the SARS-CoV-2 pandemic, it is vital that laboratories participate in an EQA scheme that adheres to the ISO/IEC Guide and ISO/IEC 17043:2010 to ensure optimum performance of analytical laboratories, including instrumentation, and the competence of the analytical personnel.

While diagnostics has always played an essential role, we are now in an era where diagnostics is vitally important to aid in reducing the mortality rate from SARS-CoV-2. As such, accurate and reliable controls and reagents are even more vital to clinical lab results. In addition, superior assay methodologies can aid in the early identification of adverse outcomes, enabling timely and effective treatment plan implementation. In doing so, quality control, both internally and externally, are vital to ensure optimum performance of assays, instrumentation, laboratories, and personnel.

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Utilizing phlebotomists to obtain blood samples through PIVCs

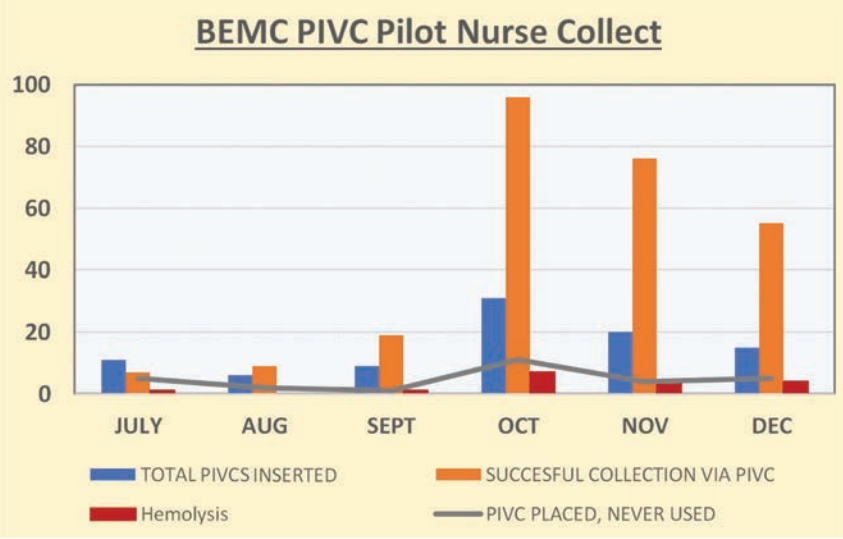
By Chuck Ramirez, BA, RTT, VA-BC; Mike Schubmehl, BSN, CCRN, CNML; Esther Valdez (ENFJ)

Even though there are nearly 200 million peripheral intravenous catheters (PIVC) placed in patients in the United States annually,[1] the healthcare industry has been slow to accept the process of utilizing catheters as a conduit for drawing blood specimens. It has taken nearly four decades of analyzing the sampling of blood through PIVC to finally demonstrate positive results.[2] Initial concerns were many, from simple inconsistencies in clinical practice to biochemical errors.[2,3]

As the research data improved around blood collection from PIVC, organizations or departments that steer the management of PIVC changed. In 2011, the nursing standards of practice for infusion stated that sampling blood through short peripheral catheters has been found to be reliable.[4] With these types of standards now the norm, there has been a wave of blood collection through various types of PIVC.[5]

Creating a pilot program

To improve the patient experience, Banner Estrella Medical Center (BEMC) – which is owned by 28-hospital Banner Health in Phoenix, AZ – created a steering team of laboratory, nursing, and vascular-access specialists to create a PIVC blood draw pilot on a nursing unit at BEMC. The initial design was to implement the pilot utilizing nurses to do 100 percent of the PIVC blood collection, utilizing a controlled area and specific supplies to limit the variables. The initial phase of the pilot was to identify successful blood-specimen collection processes without experiencing any adverse outcomes.



Nurse sample collection graph represents successful collection through a PIVC by nursing over six months. Over time successful collection through the PIVC improved without significant change in hemolysis.

For the second phase of the pilot, BEMC wanted to expand to a larger area of the hospital. However, the committee realized that nurses did not have time to take on an additional task of collecting all blood samples. As a result, the pilot steering team decided to evaluate the feasibility of using a centralized phlebotomy team, which was already on hand, to collect the samples. This would also allow for continuity in the blood-sample collection process. If phlebotomists are not successful in PIVC sample collection, they could use a standard venous method – a task nurses do not perform – and not delay patient care.

The nursing phase

In the first phase of the pilot, the nurses in specific units were given training in PIVC blood collection. Special signage was created to let everyone know that this patient could have PIVC blood collection. Laboratory would then be notified of the collection site. Over several months of nurse collection, the pilot was very successful. The nurses had achieved a 60 percent sample-collection success rate, with minimal specimen errors.

However, the initial data also showed that there was some room for improvement because the nurses did not collect patient specimens successfully 40 percent of the time. After reviewing the data in more detail, the steering team also discovered that several patients had the correct PIVC, but it did not get utilized for sample collection because of failed communication. In addition, sample-collection success varied, depending on which nurse was assigned to the task.

However, the biggest issue for nursing was the added procedure time necessary for sample collection. As the steering team members looked forward to a possible pilot expansion, they knew the time needed for sample collection would be a problem. They realized that as nursing ratios (or the patients per nurse) increased, so would the risk that missed attempts would increase. As a result, the steering team decided to move to the next phase of the pilot using phlebotomists for sample collection.

Phlebotomy phase

From the steering team's perspective, the logical and most qualified individuals to collect samples from PIVC would be the phlebotomists. However, use of the PIVC from any professional group other than nursing was not the norm at BEMC. Early in the process, the steering committee had looked at external research to find out what other professional groups perform PIVC blood collection, finding that numerous unlicensed professional groups are collecting samples in this format, including anesthesia techs and emergency department techs, to name a few.[5]

Historically, phlebotomy had not been permitted to collect samples via any other method other than venipuncture/capillary draw. But after reviewing nursing statues and clinical laboratory standards, the steering team did not discover any legal issues that would prevent phlebotomy from performing this task.[6,7] Another issue the team identified was the concern around whether phlebotomy would be able to flush the PIVC after completing the sample collection. To clarify that point, the team asked the pharmacy department if saline was classified as a medication. Pharmacy's perspective was that flushing a PIVC is a mechanical device and does not involve medication administration, meaning that phlebotomists may perform that task.

The pharmacy department said its conclusion was based on a review of the U.S. Food and Drug Administration (FDA) product

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BEMC PIVC Pilot Project - Phlebotomist Collecting Samples Off of a PIVC								
Dates Included in Data	Total Possible Known Phlebotomy PIVC Collections	Total Successful Collections	Total of Combined Missed Collection Opportunities From PIVC	Total of Missed Phlebotomy Collection Opportunities from PIVC	% of Functioning PIVC's for Specimen Collection from Lab	Avg Age (Yrs) of Patients with collection via PIVC	Total Cancelations due to Specimen Integrity	% of Total Successful Collections without Integrity Issues
11/21-11/30 Training Began	11	10	1	1	91%	NA	0	100%
12-2/12-31	155	138	17	9	94%	NA	0	100%
1-1/1-31	116	112	4	1	99.14%	NA	1	99.11%
2-1/2-29	119	108	11	5	95.38%	NA	0	100%
3-1/3-31	121	114	7	5	95.62%	63	0	100%
Pilot Success Rate (Not Including Training Dates	511	472	39	20	95.80%		1	99.79%

The chart represents data from a 4-month period in which phlebotomist were utilized to draw specimens from PIVC. During the data collection period phlebotomist experienced a 92% success rate.

classification, which lists a saline flush as a 510(k) product.[8] Following an extensive review of statues and expert legal opinion, the team determined that there was no legal reason preventing phlebotomists from collecting samples via PIV and flushing the catheter.

Following the approval process, a training course for phlebotomists was developed and implemented. This included everything from biology concepts and historical background to flushing technique. Initial training included completion of a four-hour didactic course followed by precepting with a qualified nurse. Precepting included five successful sample collections via PIVC. Completion of the didactic training and the nurse preceptorship allowed the phlebotomist to collect samples from the PIVC on their own.

Pilot review

Following the training for phlebotomists, the pilot began on the same hospital units where nurses had previously implemented the pilot. After several months, the steering team expanded the pilot to multiple floors of the hospital because the phlebotomy team had collected the samples successfully. A bonus to having the phlebotomy team using the PIVC for collection is that if it was unsuccessful, the phlebotomist has the skill set to try again with a traditional sample collection method. This allowed for zero downtime from an unsuccessful PIVC collection to a venous collection if needed. In the initial pilot period, the nurse would have to submit a request for a venous sample collection to the phlebotomy department if the PIVC collection was unsuccessful, leading to a delay.

Data collection results gathered over a four-month period showed an improved PIVC sample-collection rate utilizing phlebotomy, compared with that of nursing. As mentioned earlier, the collection success rate during the nurse collection period using the same PIVC averaged 60 percent. Using phlebotomy, the success rate for PIVC sample collection averaged 92 percent. During this period, there were no incidents of hemolysis for samples collected. The team had one sample clot out of 472 PIVC collections.

An additional outcome measure was the impact of the sample collection process on the patient experience. A three-question survey was designed to ask patients about their blood-draw experience. The results: One hundred percent of patients said they would prefer their blood be drawn from the PIVC if admitted again. Although the survey is a subjective measure, it does reflect the patient experience as a positive point.

Conclusion

The results for the use of a PIVC for blood collection by a trained phlebotomist are favorable. Success rates of 92 percent without venous complications is a compelling outcome. The entire pilot from nurse collection to phlebotomy collection was approximately nine months in length, and although the pilot is facility-specific and may have internal biases, standard methodologies were utilized for sample collection. The evidence generated during the pilot was strong enough that BEMC moved from a pilot phase to standard practice, including expansion to other facilities within the healthcare system.

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Technology looks to support best outcomes in oncology testing for women

By Lisa-Jean Clifford

In the past few years, new technology advances and a focus on oncology testing have been hot topics in digital pathology, artificial intelligence (AI) and image analysis. In addition, cancer rates have been steadily increasing despite the breakthroughs in personalized medicine and treatment plans.

In 2019, over 268,000 new cases of breast cancer were diagnosed in women in the U.S. alone, and it is the second-leading cause of death among women. Similarly, ovarian cancer causes more deaths each year than any other gynecologic cancer in the U.S. These numbers are staggering and put a spotlight on the time, resources and dollars invested in research and development of technologies and methodologies to help reduce those numbers and improve the odds of survival for patients who are diagnosed with these, and other, cancers.

Focused areas of research

When it comes to breast and ovarian pathology, there are three main areas of focus for research and technology development:

1. Developing the technology and the tools that support a faster time to diagnosis.
2. Tools that will aid the pathologist in doing mundane, time-consuming tasks that a computer can do faster and with precision, such as calculations and identification of specific types of cells.
3. Developing and determining the best applications for tools that better identify the specific types of cancer cells and other personal identifiers that will provide personal markers for better response to specific types of treatment. This will also quickly rule out treatments that will not have a positive or intended outcome.

According to the American Cancer Society:

- **Stage 1** breast cancer - When breast cancer is detected early, and is in the localized stage, the 5-year relative survival rate is 100 percent.
- **Stage 2** breast cancer - the five-year survival rate is 93 percent for women who have completed treatment.
- **Stage 3** breast cancer - the five-year survival rate is 72 percent for women who have completed treatment.
- **Stage 4** breast cancer - the five-year survival rate drops to just 22 percent with the median survival at three years. Between 20-30 percent of women with early stage cancer will go on to develop metastatic, or stage 4 cancer, and 40,000 women will die each year.

Historically, breast cancer diagnosis begins with traditional scans such as ultrasound, mammography, MRI, PET, or CT scan. If a tumor or abnormal cells are detected, a biopsy is performed. There are different types of biopsy that are indicated based upon the original findings. They can be fine-needle aspiration, which uses a small needle; core needle biopsy, which uses a larger needle; MRI-guided biopsy; or surgical biopsy, in which all or part of a growth is removed and analyzed for cancer. Fine-needle aspiration and core needle biopsies may be performed using imaging, such as ultrasound, breast MRI, mammography, or CT scan.

Once the sample has been taken, it is sent to the laboratory for interpretation and diagnosis. This process is crucial not only for a diagnosis, but also for the turnaround time for the diagnosis. The grading and determination of the specific type of tumor and cancerous cells dictates targeted therapy or other personalized treatments. These findings, and the speed of diagnosis, is what determines the best course of treatment for the patient and drives the best outcomes. The earlier cancer is detected, the earlier treatment can begin, and the better the outcome for the patient.

Digital pathology and algorithms

Digital pathology speeds the time to diagnosis and provides pathologists with access to patient case information and whole slide images electronically and in an automated, integrated environment. This helps the pathologist by providing all the information they need to diagnose a patient quickly and accurately and enables the instantaneous distribution of that information back to the ordering clinician. Efficiency gains have been seen in the 20-40 percent range based upon studies done by labs that have implemented digital pathology.

There are artificial intelligence (AI) algorithms that can be integrated directly within the digital pathology workflow that provide the pathologist with rapid results. These results can identify and highlight items like breast cancer types – from triple-negative, inflammatory and metastatic to luminal, HER2-positive and more. There are algorithms that have been built for standard protocols – including ER/PR, Ki-67, HER2, P53, and PD-L1 – and there are algorithms that have been built for more esoteric or proprietary panels and assays.

Algorithms can also help with expeditiously locating regions of interest to aid pathologists by directing them to a specific area of the specimen, and can perform counts and calculations that determine the staging and grading of the tumor – all contributing to early and specific detection.

Ovarian cancer testing

Ovarian cancer testing is another area of focus for technological advancement. While it is the fifth-leading cause of death in women, it is very difficult to diagnose ovarian cancer early. There are three main types of ovarian tumors:

- **Epithelial tumors:** These tumors are the most common type of ovarian tumors and originate from cells that make up the outer surface (epithelium) of the ovaries.
- **Germ cell tumors:** These tumors originate from cells that produce eggs.
- **Stromal tumors:** These tumors originate from cells in the ovarian stroma. Stromal cells connect the parts of the ovary together and secrete female hormones.

Biopsy is also the method used to interpret cells and provide a diagnosis for ovarian cancer. It is the leading form of

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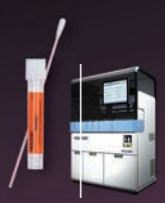

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gynecological cancer in women. There are two methods of performing a biopsy for this form of cancer:
1. Laparotomy - The surgeon cuts into the abdomen and examines the abdominal organs.
2. Laparoscopy - The surgeon inserts a thin tube through a small cut in the abdomen. This procedure can be used to remove small benign cysts or ovarian cancer in its early stages. This method is also used to see if the cancer has metastasized into other areas.

There are also image analysis and AI algorithms that can identify specific biomarkers. Biomarkers indicate the presence (or potential for the presence) of a specific disease.

There are also biomarkers that can be indicated for therapeutic use in ovarian cancer. Digital pathology with integrated AI and image analysis algorithms can quickly identify these and bring them to the attention of the pathologist. There are some common biomarkers identified as being linked to different forms and functions in ovarian cancer:
1. BRCA1 - hypermethylation of this gene is found in 10-15 percent of ovarian cancer cases.
2. MLH1 - methylation of this gene's promoter can be determined as indicative of the resistance to platinum-based treatments for epithelial ovarian cancer.
3. HOXA9 - hypermethylation of this gene's CpG promoter is found in cancer cells, including ovarian cancer.

The Institute of Cancer Research in London built an algorithm that looked for differences in tumor cell shapes. It found that a misshapen nuclei was indicative of a more aggressive form of ovarian cancer with a survival rate of only 15 percent over five years. This is another way that AI and image analysis can aid in a faster diagnosis, determination of specific cancer types and help provide a pathologist with information that is key to better outcomes. A computer program would be better able to quickly identify minor, almost imperceptible changes in shapes and highlight those for the pathologist to focus on.

Conclusion

Breast cancer is ranked first in new cancer diagnosis, and ovarian cancer is ranked as the sixth-highest for cause of death among all races, ethnicities and among both male and female.[1] That is a scary figure considering that ovarian cancer is a major concern for half of the world's population.

Given those statistics, it is understandable why the focus of technological advancements in pathology is on digital pathology, AI and image analysis as they support a faster diagnosis and increase accuracy when combined with the expertise of a pathologist. As digital pathology becomes more widely adopted, we can hope for faster diagnoses and more prevalent application of personalized, targeted treatment and better outcomes for the patient.

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Education and training remain key to safely operating centrifuges

By Linda Wilson

Image by Scotth23 Courtesy of Pixabay

Centrifuges typically have a fixed-angle rotor or a swing-out rotor, which is pictured here.

Human error is the culprit behind most centrifuge accidents in labs, according to the Occupational Safety and Health Administration (OSHA). This means that lab managers can improve centrifuge safety at their organizations by refining operating and maintenance procedures and emphasizing staff training.

As the name centrifuge suggests, these machines use centrifugal force to separate substances. Because they operate at high speeds typically by spinning a rotor around an axis, accidents can occur if users do not follow safety steps and adhere to manufacturers' maintenance recommendations.

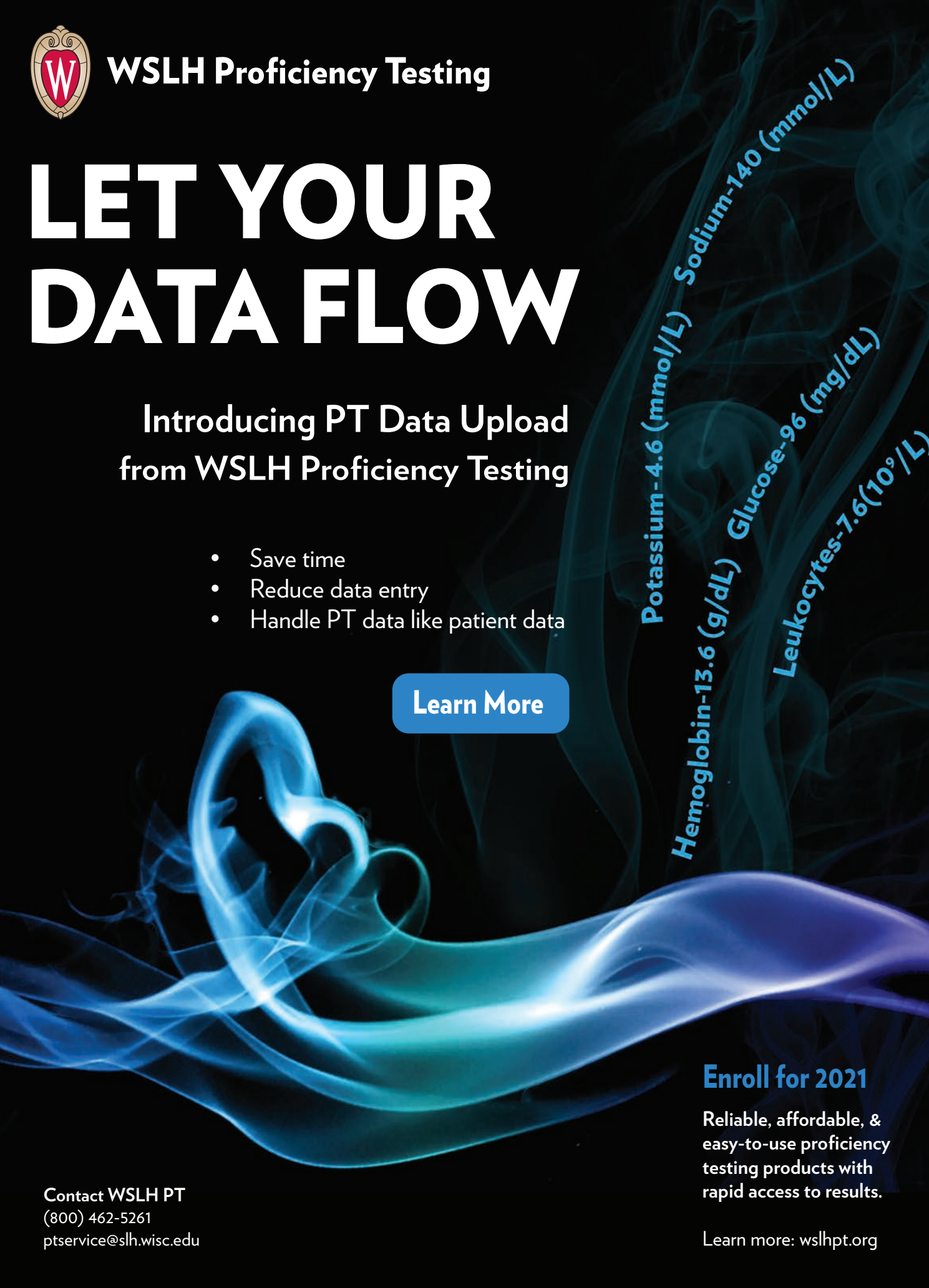
One example is an accident at a lab at the Massachusetts Institute of Technology (MIT), which occurred in 1999. In that case, no one was hurt. The centrifuge rotor split down the middle, causing the machine to cease operating and automatically lock the lid, which was later opened by a technician working for the manufacturer. Although it was impossible to pinpoint the cause of the accident precisely, the technician concluded that the ages of both the rotor, which was long past its manufacturer's recommended lifespan, and the centrifuge were to blame.[1]

"The most common accidents involving centrifuges involve tube breakage, many times springing from a tube imbalance. Other issues include imbalances that move the centrifuge (sometimes off the counter and onto the floor!), injuries from staff opening centrifuges (older models) before they are stopped, and electrical issues (frayed cords, etc.)," according to Dan Scungio, MT(ASCP), SLS, CQA(ASQ), better known as Dan The Lab Safety Man, a consultant based in Williamsburg, VA.

Nonetheless, centrifuge accidents are typically relatively minor, according to Scungio. "As a lab safety officer covering multiple labs, I can tell you that centrifuge accidents are not a daily occurrence. Many accidents are not reported, especially if they do not involve employee injury or exposure. Staff members shut off the centrifuge if it is imbalanced, they clean up spills or breakages, and move on with their day," he said.

Yuliya Mikhed, PhD, Applications Specialist for Centrifugation Laboratory Products at Thermo Fisher Scientific, added that "centrifuge accidents are quite rare. There are a lot of norms and regulations that centrifuge manufacturers need to comply with before the unit can even leave the R&D floor. Regulations describe very precisely all safety features that need to be implemented to prevent any severe consequences from potential accidents," she said.

For example, Mikhed said, in an unlikely event of a centrifuge crash – when parts of the centrifugation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system, such as rotors and buckets, disintegrate – centrifuges are designed to contain all elements, so that particles do not escape from it.

There are other common safety features in newer models, Scungio said. "Most centrifuges are designed so that they cannot operate while the lid is open. Some newer models are equipped with automatic rotor recognition. This allows the centrifuge to detect a newly inserted rotor and automatically limits the speed (rpm) to the rotor's maximum permissible value. Newer models alert users quickly when they sense load imbalances or other issues, and they will stop running to prevent a major incident," he said.

But that does not mean that laboratory managers should be complacent, and there are steps they can take to prevent problems.

Safe operating procedures

Before operating a centrifuge, staff members should make sure it is properly balanced and secure on a level surface with at least a 6-inch clearance at the sides and 4 inches at the rear of the centrifuge, the Centers for Disease Control and Prevention (CDC) recommended.

Staff members also should ensure that the centrifuge bowls and tubes are dry, the spindle is clean, and the rotor is properly seated on the drive shaft, according to OSHA.[2]

Balancing the load also is crucial, particularly if the machine will be only partially full. Eppendorf, a manufacturer of centrifuges, offered these tips on its website for load balancing:[3]

- For fixed-angle rotors – which hold tubes in a fixed angle – balance the tubes according to weight, loading the rotor symmetrically by both type of tube and mass.
- For swing-out rotors – which have multiple buckets that are not fixed to the rotor – load all rotor positions with buckets at equal weight and make sure tubes or plates are symmetrical. If the buckets do not swing smoothly, clean them and apply grease.

As Eppendorf explained on its website, "Incorrect loading can reduce the lifetime of the rotor, and uncontrolled, heavy vibration can lead to permanently damaging the centrifuge. More importantly, however, an imbalanced load can injure you or someone else. In the worst case, an imbalance can lead to a rotor crash."

According to OSHA, staff members should inspect tubes or containers for cracks or flaws before using them, and they should not over fill them. They also should inspect o-rings, adapters, and caps for signs of wear or damage.

Once staff members start the equipment, they should stay until the centrifuge reaches the maximum rpms without balance issues or noises, Scungio recommended. When the operation is complete, they should not open the lid until the rotor has stopped completely.

Waiting before opening the lid allows the aerosols time to settle in the case of a broken tube. Because staff members may not know if a tube has broken, Eppendorf suggests they wait at least 10 minutes before opening the centrifuge, and 30 minutes if they know that a tube has broken, according to the company's website.

OSHA noted that it is particularly important to wait at least 10 minutes after the rotor comes to a complete stop if the tubes contain infectious materials.

Steps for Operating Centrifuges Safely

1. Ensure centrifuge bowls and tubes are clean and dry
2. Ensure the spindle is clean
3. Use matched tubes, buckets, and other equipment
4. Inspect tubes and containers for cracks or flaws
5. Seat rotor on drive shaft properly
6. Do not overfill tubes or containers and make sure they are balanced
7. Make sure the centrifuge is operating properly before leaving the area
8. Do not exceed manufacturer's maximum run speed
9. Do not open lid until the rotor has come to a complete stop

Source: Occupational Safety and Health Administration (OSHA).

Regular centrifuge maintenance

In addition to proper operating procedures, regular maintenance extends the life of the equipment and ensures safe operation.

"The most common mistake is irregular cleaning and maintenance," Thermo Fisher's Mikhed said.

"The most important steps are cleaning, disinfecting and usage of lubricant and anti-corrosion oil for rotors and the centrifuge chamber," she pointed out.

"We would like to mention that not all cleaning/disinfecting reagents are suitable for centrifuges. This type of equipment consists of parts made of various materials, like steel, plastic and rubber; thus, it is important to choose a proper cleaning/disinfecting solution that will neither corrode metal parts, nor shorten the lifespan of the plastic components. Usage of lubricants and anti-corrosion oil are of paramount importance not only for prolonging the lifecycle of the rotors, but also to prevent unnecessary

micro-vibrations that will have a negative effect on the most sensitive samples," she said.

The CDC recommended that labs "maintain a complete and comprehensive rotor log for every high-speed and ultracentrifuge rotor to include all user names, run dates, durations, speeds, total rotor revolutions, and any notes on rotor condition."[4] The agency also recommended that labs arrange for rotors to "have annual stress testing and a complete certified analysis," noting that many centrifuge manufacturers provide this service.

Manufacturers typically specify lifespans for their rotors, based on years in service or number of revolutions, and labs should not exceed those recommendations.

But operating and maintenance procedures will not be successful without adequate education for staff members.

For example, the CDC recommended that lab employees have "documented training and competency assessments on each type of centrifuge they operate. Documented instruction for each centrifuge type includes proper instrument startup and shutdown, emergency procedures and shutdown, balancing of tubes, use of safety cups and covers, rotor and container selection, requirements for high-speed and ultracentrifuges, and container fill-height limitations."[4]

As Scungio said, "Consistent training for end users on the equipment's safety features remains key."

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Independent controls add value to qualitative COVID-19 antibody tests

By Patricia E. Garrett, PhD

In today's clinical lab environment, tests being utilized for the detection of SARS-CoV-2 antibodies are not only new to a lab but are also new for the manufacturers, the regulators, and the lab industry as a whole. Common sense and QC (quality control) experts tell us that our newest or weakest tests or instruments are where we need to concentrate on quality control. As such, antibody tests for SARS-CoV-2 certainly qualify for extra attention.

Serology tests as qualitative assays

One novel aspect for some labs is that these are qualitative tests. The most common definition of a qualitative test is one that produces binary results, often positive/negative. A better definition is that a qualitative test has only one medical decision point, and that medical decision point is the cutoff.

Also, the anti-SARS-CoV-2 test is a serology test, an assay that has been carefully designed and manufactured to provide one simple output – often a signal-to-cutoff (s/co) ratio or a color that indicates the presence of antibodies to this specific virus. The secret behind the simplicity is that humans can make lots of different antibodies to the same virus if the virus has many different proteins associated with it. Depending on its design, a qualitative serology test for anti-SARS-CoV-2 may be looking for antibodies to some piece of the virus's spike glycoprotein (S) or its nucleocapsid phosphoprotein (N), IgG, IgM antibodies, either or both, to either or both of these antigens, all with one s/co result.

Quality control for qualitative tests

Controls for qualitative tests monitor the accuracy and precision at the cutoff or the medical decision point. But what does that mean exactly? The Clinical Laboratory Standards Institute (CLSI) document *User Protocol for Evaluation of Qualitative Test Performance*[1] calls the cutoff C_{50}, because a sample with a s/co response of 1.000 should test positive 50 percent of the time and negative the other 50 percent, with normal imprecision or variability in the response. As you move away from C_{50} toward a higher s/co, the percentage of positive results increases along with the analyte concentration, until 100 percent of results are positive. The opposite is true as you move away from C_{50} toward a lower (<1.0) s/co.

Accuracy or bias is measured as a shift in the location of the cutoff away from C50 under varying conditions (e.g., on different days or in different runs), as illustrated in Figure 1A.

The boundaries in **Figure 1**A have been set as C5 to C95. C5 is the point at which only 5 percent of samples with a mean s/co of 1.00 would still yield a positive result. C95 is the point at which 95 percent of samples with a mean s/co of 1.00 would yield a positive result.

Precision is measured as the distance along the x-axis that describes the run-to-run variability or random error in the cutoff.

Figure 1B illustrates imprecision in two methods. The solid red line represents a more precise method, where

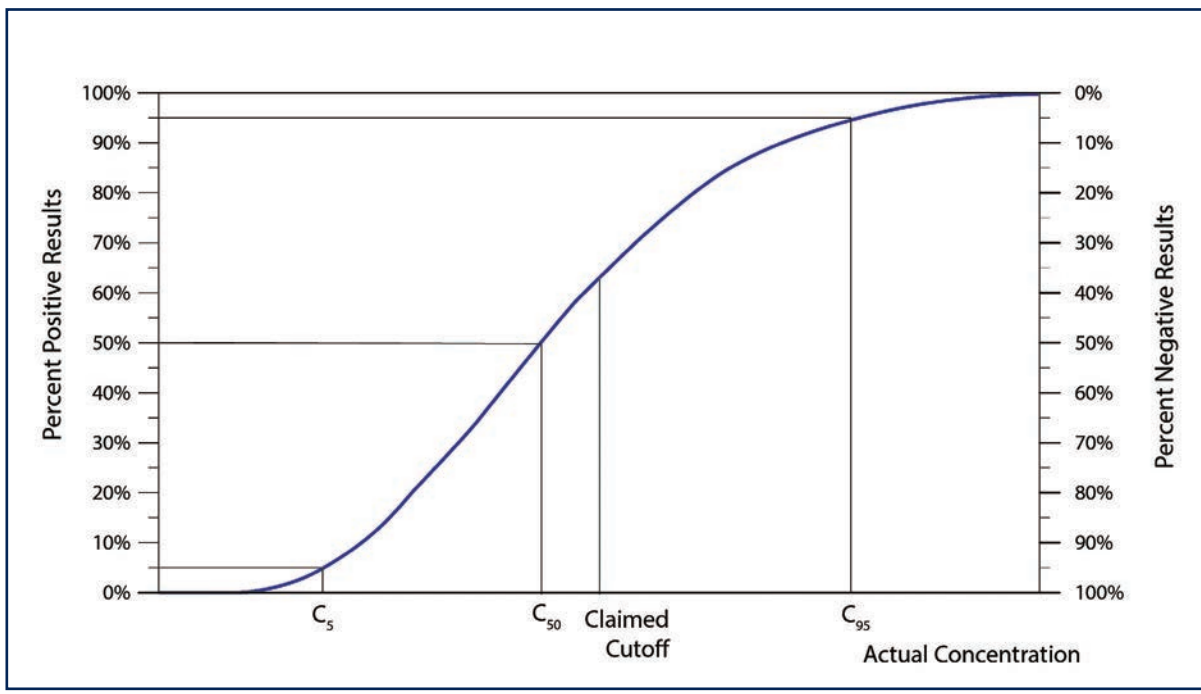

Figure 1A. Analyte Concentration Near the Cutoff. The percent of positive and negative results from a large series of test results would be expected to change as a function of the analyte concentration near C_{50} See reference 1.

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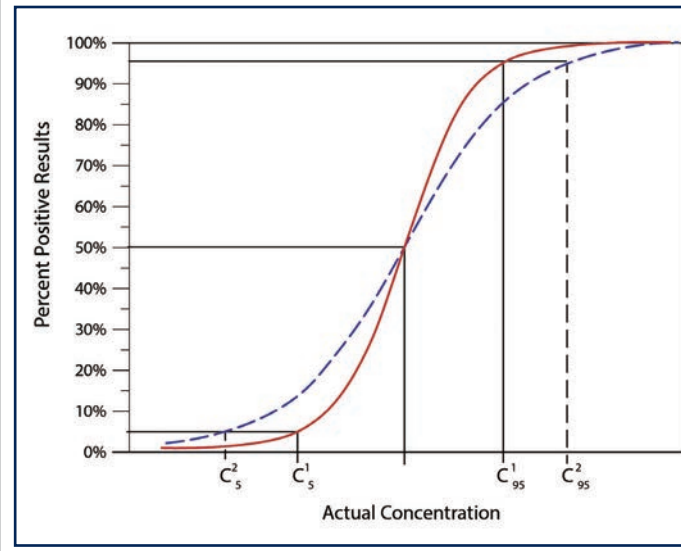

Figure 1B. Examples of Different Imprecision Curves. Depiction of how the percent positive and the percent of negative results from a large series of test results would be expected to change as a function of the actual sample concentration near C_{50}. for two candidate methods with the same C_{50}. Method 1 (the solid red line) has a narrower C_5-C_{95} interval than Method 2 (dashed blue line). See reference 1.

the C_5 to C_{95} range is narrower, and thus the variability at C_{50} is less. The method represented by the broken blue line has a wider C_5 to C_{95} range, describing a greater variability around the cutoff.

Independent controls

The use of independent controls (aka third-party or external controls) is considered best practice for serology tests, even those that come with manufacturer supplied controls.[2] Kit controls are most commonly designed to monitor bias and precision in a specific kit lot. One major added value of an independent control is that it is designed to work across kit lots. Thus, if there is a significant shift in the cutoff with a kit lot change, or a significant increase in random error, a kit control may not see it, but an independent control should.

If the test chosen produces a numeric result (often a s/co), the independent controls can be charted to show bias as a change in the mean of sequential control observations, and a change in precision as increased or decreased amplitude of the 'spikes' in the chart.

Figure 2[3] describes a recent issue with a seemingly minor reagent change that resulted in decreased sensitivity in a commercial anti-HCV assay.

The independent control shifted when the lot with the changed reagent was introduced. A lab using an independent control noted the shift, which persisted in replacement lots, and an investigation with some naturally occurring and formulated low titer samples confirmed decreased sensitivity (false negatives) in the affected lots. The manufacturer's internal investigation found the problem and resolved it.[4]

Conclusion

Either a mean shift, or an amplitude change in an independent control, signals a change in the sensitivity/specificity of the test. As with quantitative assays, consistent variability within the established control limits signals an assay that is working as intended.

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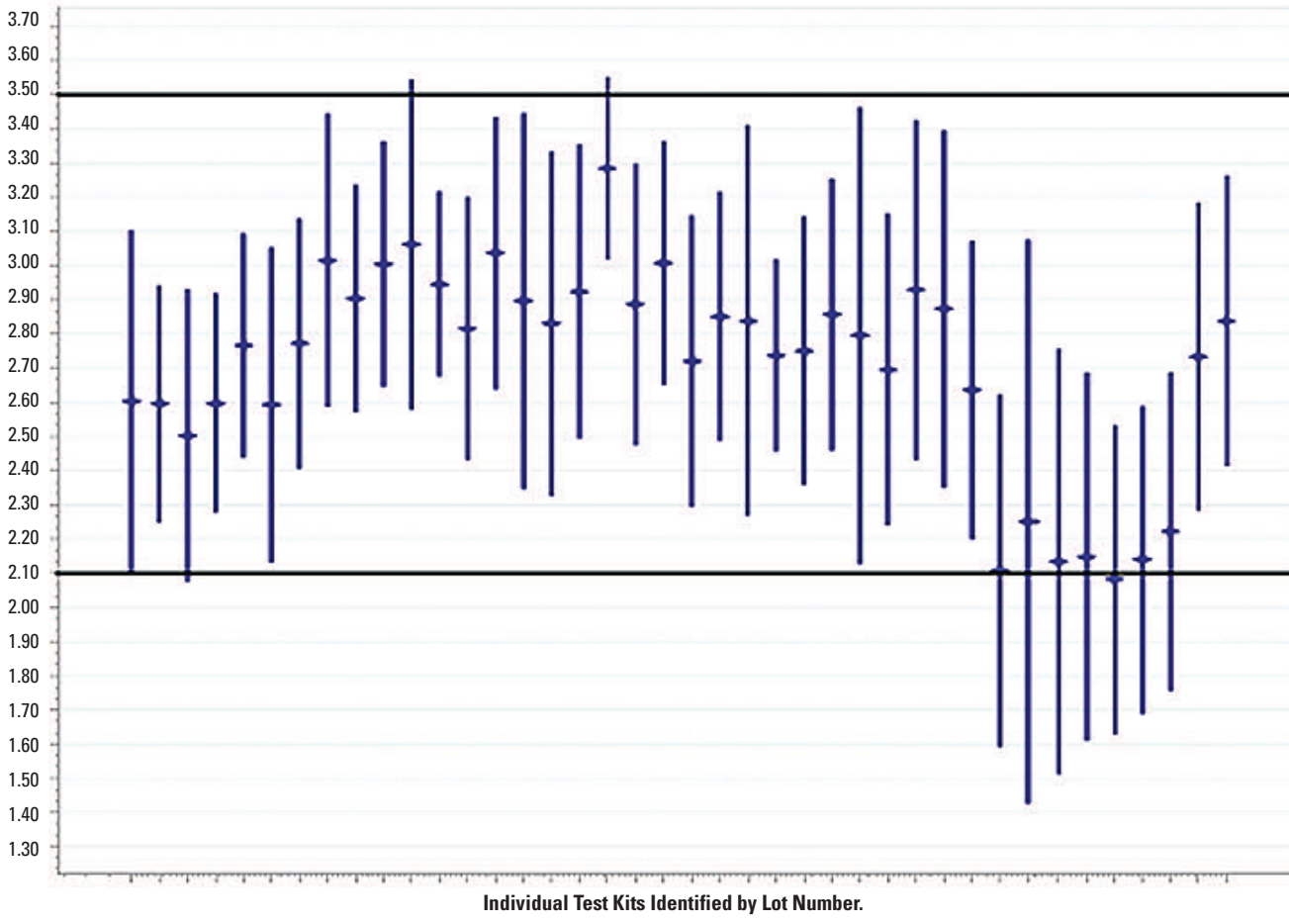

Figure 2. Representative results of independent quality control, tested in different lots of ARCHITECT HCV assay, where the central bar is the mean of the QC test results and the vertical bars represent the mean ± 2 standard deviations.
The S/Co Value is presented in the *y* axis and the assay lot numbers on the *x* axis. Horizontal lines indicate the NRL acceptance range "Connect Limits" fot he independent quality control sample testing in the Abbott Architect andit-HCV CMIA. See reference 3.

coronaviruses are common in the environment, and therefore, antibodies to coronaviruses are common too. The inevitable trade-off between sensitivity and specificity comes into play here. A highly specific test will (almost) only detect antibodies to SARS-CoV-2 and will produce very few false positives. High specificity comes at the cost of lower sensitivity – some low positives will be missed, i.e., they will be resulted as negatives (false negatives). But low positives will be relatively unimportant for clinical or surveillance purposes for SARS-CoV-2 antibodies.

Use of independent low positive and negative controls, along with the manufacturer's recommended quality control practices, will help laboratorians become more familiar with, and hopefully more confident in, novel coronavirus antibody tests, and ultimately help lab personnel detect errors.

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Patricia Garrett, is Principal at **Pat Garrett Consulting**. She has worked in hospital labs and diagnostics companies for more than 30 years, focusing on QC, method evaluation, and infectious disease tests. She led the working group that produced CLSI's EP12-A2, User Protocol for Evaluation of Qualitative Test Performance.

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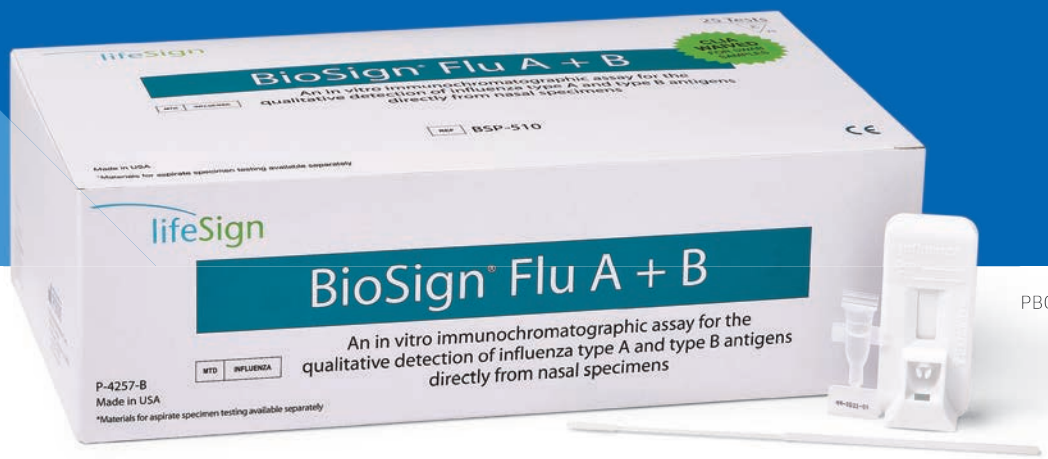

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Understanding the limitations of integrated workcells

By Anthony M. Barresi, Sr.

Overburdened and understaffed, today's core labs are being asked to continually improve their performance under increasingly stringent operational constraints. Studies estimate that as many as 8,000 more laboratory technologist graduates are needed, per year, to keep pace with demand.[1] Yet, despite this shrinking labor market, and having limited access to financial resources, labs are beset by requests from management to increase reliability, establish standardized procedures, and return results in less time – especially for STATs. Adding to this pressure is a steadily growing workload fueled by the increased healthcare consumption of an aging population.

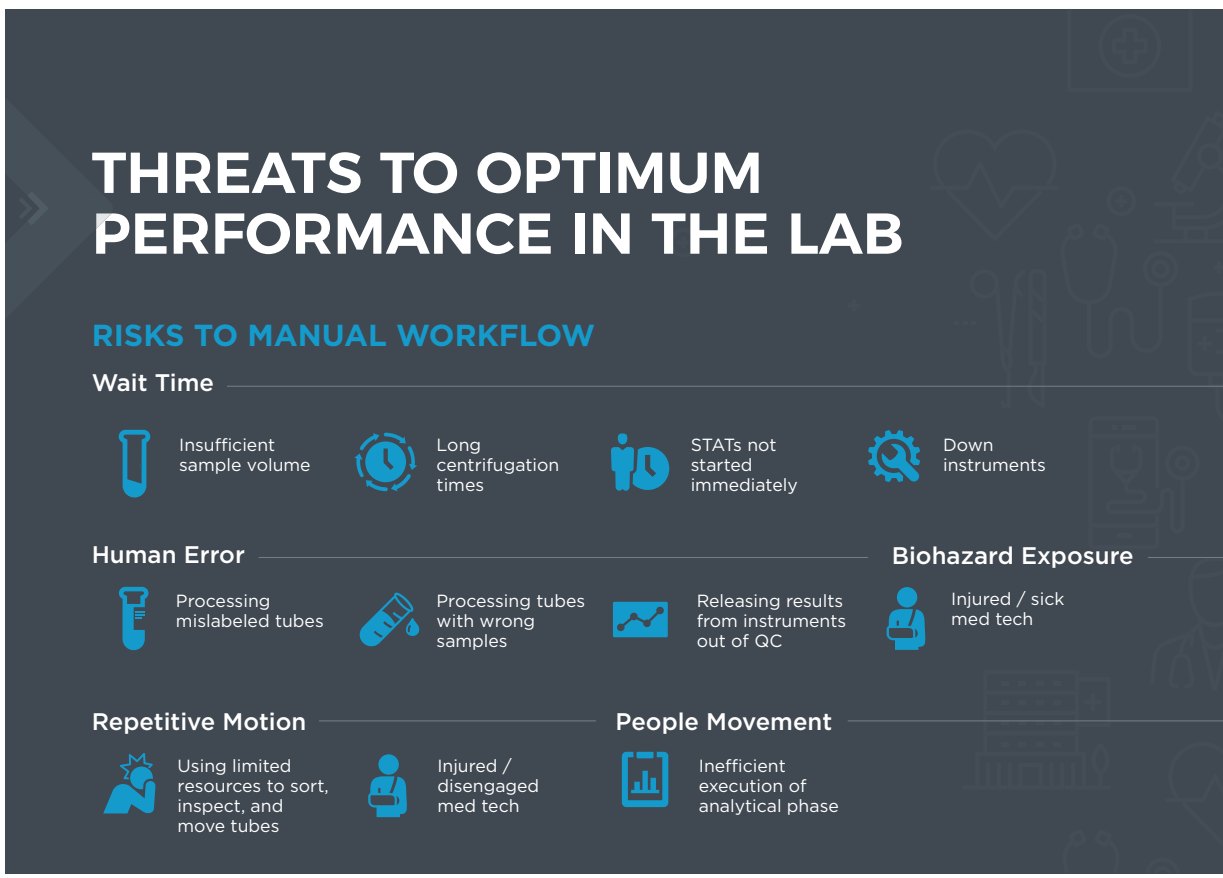
These challenges notwithstanding, hospitals, in particular, are seeking ways to drive even more value from labs while decreasing their average costs per test. This steadfast commitment is mostly owing to the fact that labs typically consume three-to-five percent of hospital operating budgets. To meet these expectations, a growing number of hospital laboratories have begun investing in total laboratory automation solutions. The advantages of total lab automation are myriad; these systems minimize human errors, accelerate turnaround times, standardize processes, protect result integrity, and maximize the productivity of limited staff resources.

So why hasn't every lab invested in a robust automation solution? The answer is simple. Most comprehensive laboratory automation solutions are too large and too expensive for the majority of today's labs. So instead, many have begun investing in what they consider to be their only option for achieving automation-enabled performance improvement: integrated workcells. Crediting the analytical efficiency gained by connecting chemistry and immunoassay analyzers within a single frame, purveyors of integrated workcells promise to deliver meaningful performance improvement at an approachable size and price point.

In reality, however, integrated workcells alone are incapable of delivering the end-to-end workflow optimization that is required to significantly improve laboratory performance. Moreover – and, most importantly – integrated workcells leave laboratories unwittingly exposed to numerous risks that, when realized, drastically outweigh any benefits provided by analytical efficiency.

Productivity risks and increased costs

While touted as a solution designed to boost productivity, integrated workcells actually leave numerous productivity risks unmitigated across the laboratory



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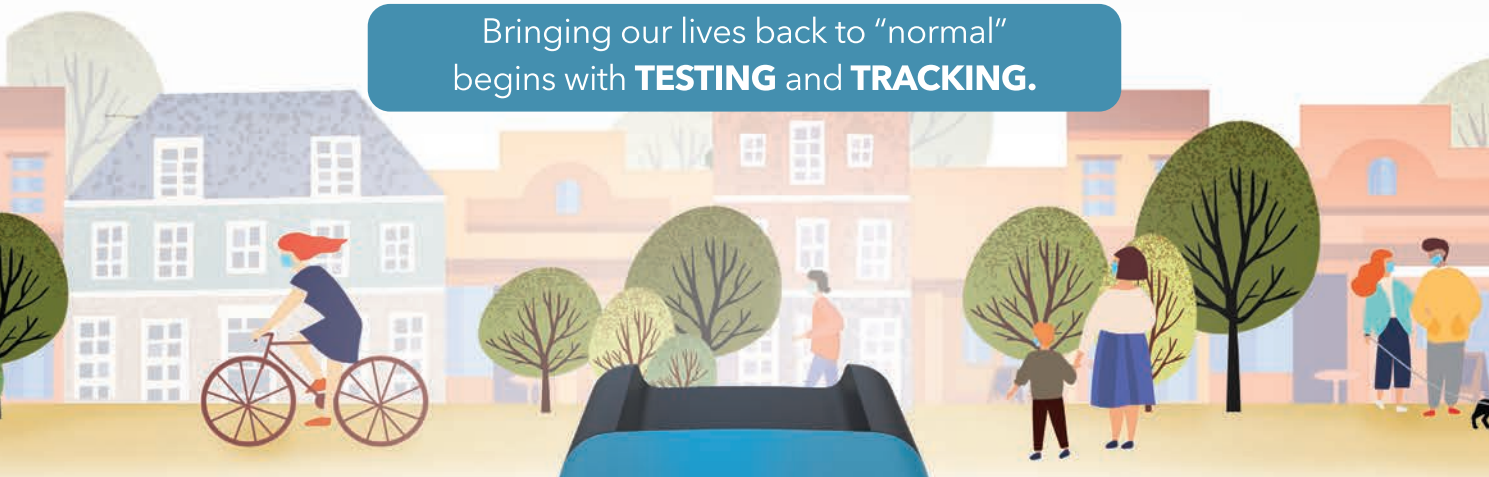

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Pre-analytical errors impact patients and cost labs, but integrated workcells do little to help.

workflow. Typically, a laboratory's workflow comprises 32 manual steps, the majority of which are completed during the pre- and post-analytical phases. An astounding 80 percent of productivity risks occur during these phases, including insufficient sample volumes, long centrifugation times, delayed STAT start times, and mislabeled samples, among others.[2] Integrated workcells, which contribute most of their value by streamlining portions of the analytical phase, do nothing to address these risks to productivity, leaving their laboratories fully exposed to the slower turnaround times and increased costs per test that inevitably result.

Protection from pre-analytical errors

Many of the risks that integrated workcells fail to address lead not only to diminished productivity, but also to diminished patient safety. An estimated 75 percent of result errors can be traced back to pre-analytical mistakes that were not caught prior to analysis. Despite that alarming statistic, today's integrated workcells deliver no pre-analytical error evaluation.[3] Instead, integrated workcells leave this important and arduous responsibility squarely within the jurisdiction of already-overloaded laboratory technologists. Given their long shifts and broad duties, and the inherent propensity for all humans to make mistakes, it is little wonder that, in this environment, many pre-analytical errors go unnoticed into the analytical phase.

Specifically, integrated workcells do little to help laboratorians identify mislabeled tubes, tubes containing wrong samples, or tubes carrying insufficient sample volumes. Such errors can put patients' safety at risk, damage the credibility and reputation of labs, and expose hospitals to liability.

Importantly, these errors can also lead to the accrual of significant operational costs. Consider that a typical "medium-sized" hospital laboratory processes around 182,500 tubes per year.[4] Studies show that approximately 0.66 percent of these tubes will come into the laboratory with one of the aforementioned errors, and that 72 percent of those tubes will directly contribute to additional costs.[4,5] How much cost? On average, $208 per pre-analytical error in the U.S.[5] Simply multiplying these factors together shows that, without enhanced help in identifying pre-analytical errors, a laboratory of this size can expect to incur approximately $180,000 per year in costs related to mislabeling, wrong samples, and insufficient sample volumes, alone.

Handling tubes and safety risks

Patient safety, hospital operating costs, and laboratory reputations are not the only things that integrated workcells do little to protect. Indeed, the safety of lab techs must also be included in this category. The reason is simple. Unlike with more-comprehensive automation systems, using integrated workcells alone means that lab staff must manually perform the majority of tasks in their lab's pre- and post-analytical workflow phases. Of course, performing these tasks manually means that techs must personally handle tubes. And the more techs handle tubes, the more their health and safety are exposed to risk.

It should come as no surprise, then, that lab techs experience high incidences of repetitive stress injuries and infection as part of their jobs. In fact, the rate of Carpel Tunnel Syndrome (CTS) among techs hovers at around 10 percent.[6] This trend is important because those suffering from CTS can be out of commission for weeks and even months as they undergo treatment and, if necessary, surgery and rehab. This not only negatively impacts quality of life for techs, it leads to lost productivity and higher costs for the labs that employ them.

With integrated workcells doing little to obviate the need for manual manipulation of tubes, techs who work in labs that have not adopted more comprehensive forms of automation can expect their risk of developing CTS and other stress injuries to remain undiminished. Furthermore, techs in such labs can expect little in the way of enhanced protection from being infected by *e. coli*, N. meningitis, Brucella, and other microbes and viruses.[7] This is because an estimated 44 percent of manual workflow steps in the lab can directly expose techs to biohazards, and integrated workcells automate very few of those steps.[8] The importance of protecting frontline healthcare workers from infection has perhaps never been more apparent than it is today, in the midst of the novel coronavirus. It is, therefore, critical for labs

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Risk of Injury Threatens Techs and Their Productivity

Integrated workcells do little to lessen the need for laboratorians to handle tubes.

to realize that integrated workcells are of little use on this front, and that more comprehensive solutions – ones that automate manual steps across all three workflow phases – are needed to achieve the enhanced levels of laboratorian protection that are especially warranted in light of ongoing COVID-19 pandemic.

Mundane work affects productivity

Among the many benefits of comprehensive laboratory automation systems is that they automate mundane, manual tasks. When a lab uses just integrated workcells, however, its techs remain forced to spend hours accessioning, inspecting, decapping, transporting, and recapping tubes. Such repetitive, rote tasks can cause disengagement to proliferate within a precious and limited talent pool. And when techs become disengaged with their work, their productivity decreases, the frequency with which they make errors increases, and laboratory operating costs rise.

In fact, studies show that disengaged employees have 37 percent higher absenteeism and 18 percent lower productivity than their engaged counterparts.[9] As a result, disengaged employees in a lab will, on average, cost that lab about 34 percent of their salaries annually. Over the course of a typical laboratory-equipment contract term, this translates to hundreds of thousands of dollars of costs incurred due to disengagement alone.[6] Unlike with integrated workcells, one of the key advantages of investing in more comprehensive laboratory automation is that such systems take over many of the lab's mundane, repetitive, and rote tasks, freeing technologists to do more of the skilled, rewarding work they love. This, in turn, increases their accuracy, productivity, and engagement.

Integrated workcells and workflow automation

Given the considerable risks to patient and tech safety, quality of results, lab productivity, and operational costs that are left unaddressed by integrated workcells, it's logical, and likely imperative, to assert that they are not effective stand-ins for systems that automate the majority of manual steps across the pre-, intra-, and post-analytical workflow phases. By leaving tubes in the hands of techs throughout the majority of the laboratory workflow, integrated workcells simply fail to address the most pressing challenges faced by today's labs. Labs must find, and invest in, more comprehensive solutions – systems that deliver the primary advantages of total-laboratory automation while accommodating budget and size constraints. Only with those solutions will labs enable themselves to consistently deliver measurably increased value for patients, employees, and hospitals.

Workflow-optimization technologies

Fortunately, the industry's most innovative and workflow-savvy vendors understand the universal need for end-to-end process optimization and, in response, have begun offering products that can deliver real performance improvement to all laboratories. They are doing so by leveraging powerful, yet affordable, cloud-computing to make state-of-the-art clinical informatics available to labs of all sizes. They are also introducing "lean total laboratory automation" solutions to the marketplace – systems that go beyond the capabilities of integrated workcells while remaining at size- and price-points tenable for most labs.

Given the significant cost, quality, and performance pressures of today's healthcare environment, comprehensive workflow-optimization tools like these are quickly migrating from the realm of "cutting-edge" to that of "absolutely essential." With this in mind, any laboratory looking to maximize return on their next capital-equipment investment would do well to ensure their technical vendor of choice includes true, comprehensive workflow optimization at the core of its proposal.

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Anthony M. Barresi, Sr., serves as marketing manager for automation solutions at **Beckman Coulter.**

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• These tests have not been FDA cleared or approved;
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• These tests have been authorized only for the detection of nucleic acid from SARS-CoV-2, not for any other viruses or pathogens; and
• These tests are only authorized for the duration of the declaration that circumstances exist justifying the authorization of emergency use of in vitro diagnostic tests for detection and/or diagnosis of COVID-19 under Section 564(b)(1) of the Act, 21 U.S.C.§ 360bbb-3(b)(1), unless the authorization is terminated or revoked sooner.

† The Panther Fusion SARS-CoV-2 assay is available for EUA use in the United States, Australia, New Zealand, and Canada. EUA does not apply to the European Union. The Aptima SARS-CoV-2 assay is available for EUA use in the United States.

‡ Aptima Zika Virus assay:
• This test has not been FDA cleared or approved;
• This test has been authorized by FDA under an EUA for use by authorized laboratories;
• This test has been authorized only for the detection of RNA from Zika virus and diagnosis of Zika virus infection, not for any other viruses or pathogens; and
• This test is only authorized for the duration of the declaration that circumstances exist justifying the authorization of the emergency use of in vitro diagnostic tests for detection of Zika virus and/or diagnosis of Zika virus infection under section 564(b)(1) of the Act, 21 U.S.C.§ 360bbb-3(b)(1), unless the authorization is terminated or revoked sooner.

¶ In development and not for sale.
§ Seeking dual claim for the HIV-1 Quant assay.

The impact of endothelial dysfunction and COVID-19 on hemostasis

By John V. Mitsios, PhD

The primary role of the endothelium is to maintain vascular permeability, blood rheology and homeostasis. Furthermore, the endothelium has several additional crucial physiological functions that play a role in setting up the innate immune response as well as exhibiting intrinsic properties involved in the activation of the adaptive immune response.[1] Recent evidence has shown that endothelial dysfunction may actively play a role in the thrombo-inflammatory process that ultimately results in Coronavirus Disease-2019 (COVID-19)-associated coagulopathy as measured by an increase in endothelial markers (i.e., von Willebrand factor (vWF), soluble P-selectin, and soluble thrombomodulin).[2]

Endothelial dysfunction has been associated with the pathogenesis and progression of various diseased states – including but not limited to – cardiovascular, renal, and metabolic complications, along with sepsis and the acute respiratory distress syndrome, or ARDS.

Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), the virus responsible for COVID-19, utilizes the angiotensin-converting enzyme 2 (ACE2) receptor on the cell membrane of the host cell to facilitate its entry. ACE2 receptors have been found in arterial and venous endothelial cells in various human tissues, including the oral and nasal mucosa, lung, small intestine, colon, skin, lymph nodes, thymus, bone marrow, spleen, heart, kidney, and brain.[1]

However, cell invasion depends on both the expression of ACE2 and the availability of the protease transmembrane protease serine 2 (TMPRSS-2), or other serine proteases, to cleave the viral spike protein.[1] The resulting infection may lead to a hyperinflammatory response, also known as cytokine storm or cytokine release syndrome (CRS), resulting in the release of pro-inflammatory cytokines such as interleukin-6 (IL-6), soluble interleukin 2 receptor (IL-2R), and tumor necrosis factor-α (TNF-α).[3] The progression to cytokine storm is manifested clinically by severe disease and the development of life-threatening multi-organ system failure.

IL-6 plays a major role in the activation of the endothelium, especially during the early phases of inflammation. Thus, IL-6 induces an increased vascular permeability, in addition to the secretion of more pro-inflammatory cytokine/chemokines by endothelial cells (IL-6, IL-8, and monocyte chemoattractant protein-1 (MCP-1)), and the activation of the complement system via C5a.[4] This significant increase in pro-inflammatory cytokines, in particular, IL-6, TNF-α, and IL-1β, which are elevated in patients with COVID-19, as well as increased vascular permeability results in the loss of the normal antithrombotic and anti-inflammatory functions of the endothelium.[5] The endothelial dysfunction as a result of the hyperinflammatory response contributes to hemostatic dysregulation, complement and platelet activation, and leukocyte recruitment in the microvasculature.

The increase in vascular permeability leads to an inflammation-mediated endothelial activated procoagulant state, as measured by vWF activity/antigen as well as considerable elevation in factor VIII (FVIII) activity.[6] The inflamed endothelium contributes to hypercoagulability by upregulating procoagulant proteins like tissue factor (TF), P-selectin, FVIII, fibrinogen, and vWF, while simultaneously downregulating natural anticoagulants such as thrombomodulin (TM) and endothelial protein C receptor (EPCR).

Further evidence of this enhanced procoagulant state is the increase in the main fibrinolytic inhibitor plasminogen-activator inhibitor-1 (PAI-1), which is known to be elevated in Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) and SARS-CoV-2, resulting in a hypofibrinolytic state.[6] Venous thrombosis (VTE) and pulmonary thromboembolism (PE) have emerged as a leading cause of death in patients with COVID-19.[7] In addition to the macrovascular thrombotic events (i.e., VTE and PE), microvascular thrombotic complications also contribute to many of the COVID-19-related morbidities (i.e., multi-organ failure).[8]

The clinical laboratory plays a critical role in the care of COVID-19 patients. The International Society of Thrombosis and Haemostasis (ISTH) has recommended monitoring certain laboratory markers in COVID-19 patients including elevated D-dimer together with PT/INR, platelet count, and fibrinogen to guide and monitor treatment in COVID-19 patients.[9] In addition, elevated D-dimer levels have been found to be the best laboratory marker to indicate thrombotic risk in COVID-19 patients. Anticoagulant therapy for thromboprophylaxis has been recommended by all major societies (i.e., ISTH, American Society of Hematology). Several randomized clinical trials are currently underway to help define optimal treatment protocols for patients with COVID-19. (A list of these studies can be found on https://www.clinicaltrials.gov/.) In addition, several other studies have begun enrollment (NCT04359277, NCT04362085, NCT04345848, and NCT04366960).

Conclusion

In summary, the hypoxia, immobility of hospitalized patients, and the sequalae associated with SARS-CoV-2 infection are potent triggers of thrombosis.

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① U.S. Food and Drug Administration. StatStrip Glucose 510K Notification K181043. Accessed online at https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm

② US Food and Drug Administration Product Classification. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPCD/classification.cfm?ID=NBW

③ U.S. Food and Drug Administration. Self-monitoring blood glucose test systems for over-the-counter use. Draft guidance for industry and Food and Drug Administration staff. https://www.fda.gov/media/119828/download

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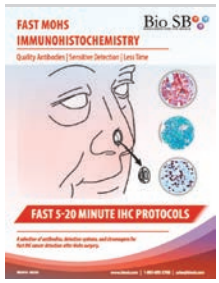

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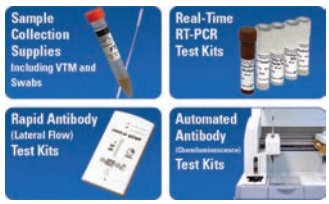

Two real-time RT-PCR test kits intended for the qualitative detection of nucleic acid from SARS-CoV-2 in nasal swabs, nasopharyngeal swabs, oropharyngeal swabs, and sputum from individuals suspected of COVID-19 have been granted EUA by the FDA. In addition to the tests, other supplies such as swabs and viral transport media are also available.

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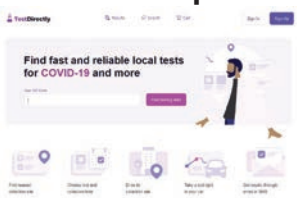
Web-based portal



TestDirectly is a web-based portal designed to help laboratories increase COVID-19 testing capacity. The portal directly links patients to collection centers and laboratories to increase the efficiency and effectiveness of COVID-19 collection, testing, and reporting. TestDirectly expedites lab services by using QR codes and mobile devices to provide rapid and remote patient data collection.

Ligolab

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The Curian benchtop analyzer features a simple, standardized, three-step workflow for easy training and implementation. The intuitive dual mode user interface can run samples in batch or as single-patient runs. The first assay launched was Curian HpSA for *H. pylori* testing, with additional assays, including *C. difficile* GDH/Toxin, Shiga Toxin 1&2, and *Campylobacter* to follow.

Meridian Bioscience

SARS Antigen FIA

The Sofia SARS Antigen FIA uses advanced immunofluorescence-based lateral flow technology for qualitative detection of nucleocapsid protein from SARS-CoV-2. The Sofia SARS Antigen FIA, with the Sofia 2 and Sofia analyzers, provides automated and objective results in 15 minutes, allowing for testing of patients suspected of COVID-19/2019-nCoV in near-patient testing environments.

Quidel

Flu A & B Test

The OSOM Ultra Plus Flu A & B Test is a CLIA-Waived in vitro rapid qualitative test that is designed to detect influenza type A and type B nucleoprotein antigens. It provides rapid results at the point-of-care (POC) with sensitivity that meets or exceeds reader devices without the need for an instrument.

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LABORATORY INNOVATOR

Early career in food chemistry grows into enzymology-based diagnostics company

By Brenda Silva

Chong Yuan, PhD, is the managing director and co-founder of **Diazyme Laboratories**. Known as a leading enzymologist, he is the inventor of over 30 U.S. patents covering Diazyme product technology.

After a career that started in food chemistry and agriculture you began Diazyme in 1999, which has had 30 patents granted in 20 years. When deciding to begin your own company, was there something that drew you from your original area of study and expertise to the clinical lab industry and diagnostics?

My training and expertise are in enzymology, beginning with my graduate school and followed by my post-doc research, as well as my pharmaceutical research experiences. Since one of the major platforms in clinical diagnostic testing is enzyme-based assays, it was very natural for me to apply my enzymology knowledge in assay development to clinical diagnostic applications.

As a professor at the University of Kansas in the Department of Pharmaceutical Chemistry, as well as senior scientist at Tanabe Pharmaceuticals, how did those experiences assist you when you decided to start your own diagnostics company? What were your takeaways from the earlier experiences?

My research projects both at the university level and in the pharmaceutical company were enzyme-based drug design. The projects utilized my enzymology skills to elucidate the drug and enzyme target reaction mechanism, and design more potent enzyme inhibitors as potential drug candidates. The idea of substrate-trapping enzyme technology was conceived while I was working on a drug design project in the pharmaceutical industry.

When Diazyme began in 1999 with "substrate trapping enzyme technology to measure small molecular biomarkers such as homocysteine, hormones, and vitamins," what did you envision beyond that for the future of the company, based on the needs of the lab industry at that time?

We know that small molecules do not have immunogenicity, and therefore, it is hard to raise antibodies against small molecules for immunoassay uses. To solve this problem, I specifically engineered enzymes that retain their substrate binding affinity and specificity, but have their catalytical activity abolished, which may serve as small molecule binders (substrate trapping enzyme) for use in small molecule biomarker assays. In the human body, there are a lot of metabolites that are small molecules and they act as important surrogates of diseases that need to be controlled. Therefore, there is always a need in clinical diagnostics for a better method to detect small molecular biomarkers.

In your opinion, what is the most challenging issue currently facing the clinical lab industry, and can you suggest any possible solutions to address how to eliminate the problem?

One of the challenges in clinical diagnostics is to identify specific biomarkers for specific diseases using specific and robust assay methods. More basic academic-level research is needed to identify more disease-related biomarkers that can help make early and accurate diagnosis of diseases a reality.

Looking to the near future and the COVID-19 pandemic, what do you see as a probable and/or viable way to slow the reported case numbers that are increasing on a global basis?

Regarding the prevention of COVID-19, practicing social distancing and wearing face masks have proven to be effective and are something everyone can do. Fast turnaround time in reporting test results is the key to reducing the spread of the disease. When a vaccine is ready for the general population, neutralizing antibody tests will be highly in demand for confirmation of the effectiveness of vaccines in each vaccinated individual to make sure a sufficient amount of neutralizing antibodies have been generated in the body to fight off the viral infection.

Where do you see the clinical lab industry in the next five to 10 years in terms of the increased use of automation and artificial intelligence (AI) in the lab?

Lab automation is an ongoing process, and more and more large- and medium-sized clinical laboratories will be equipped with fully automated lab testing systems to improve the efficiency of lab operations and cost savings, as well as to improve test result turnaround time and test quality. Eventually, fewer and fewer manual steps will be involved in lab operations. Artificial intelligence (AI) will help leverage human knowledge, wisdom, and experience. Instead of replacing doctors, AI algorithms might work best alongside them in healthcare.

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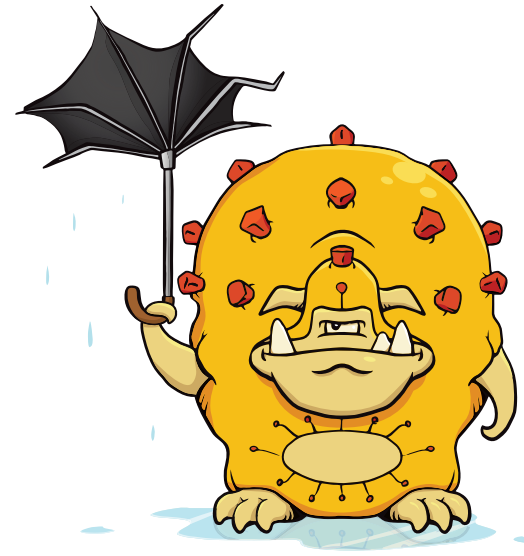

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