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CE

Utilizing Ct values in patient management decisions

State of the Industry: clinical analytics

Sepsis diagnosis options

SARS-CoV-2 and vascular dysfunction

LAB INNOVATOR

Bill Whitmar, MS
Director
Missouri State Public Health Laboratory

F E B R U A R Y

Black History

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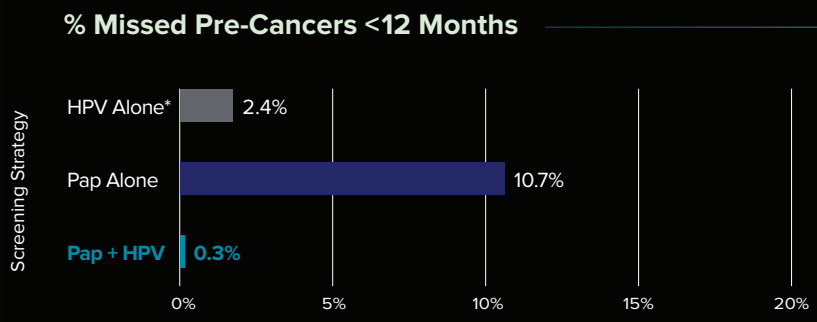

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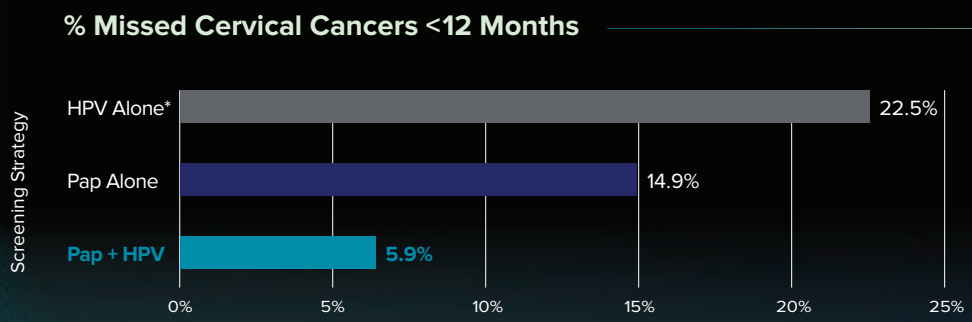

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* A positive HPV screening result may lead to further evaluation with cytology and/or colposcopy.

References: 1. U.S. Cancer Statistics Working Group. U.S. Cancer Statistics Data Visualizations Tool, based on 2019 submission data (1999-2017): U.S. Department of Health and Human Services, Centers for Disease Control and Prevention and National Cancer Institute. Released June 2020. Accessed December 22, 2020. www.cdc.gov/cancer/dataviz **2.** Kaufman H, et al. Contributions of Liquid-based (Papanicolaou) Cytology and Human Papillomavirus Testing in Cotesting for Detection of Cervical Cancer and Precancer in the United States. *Am J Clin Pathol.* 2020;XX:0-0 DOI: 10.1093/AJCP/AQAA074 (Study included ThinPrep Pap test, ThinPrep Imaging, SurePath Pap test, SurePath Imaging, Aptima HPV and Hybrid Capture 2). **3.** Austin RM, et al. Enhanced detection of cervical cancer and precancer through use of imaged liquid-based cytology in routine cytology and HPV cotesting. *Am J Obstet Gynecol.* 2018;150(5):385-392. doi:10.1093/ajcp/aqy114 (Study included ThinPrep Pap test, ThinPrep Imaging, Digene HPV, Cervista HPV and Aptima HPV).

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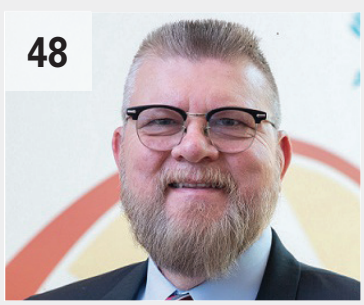

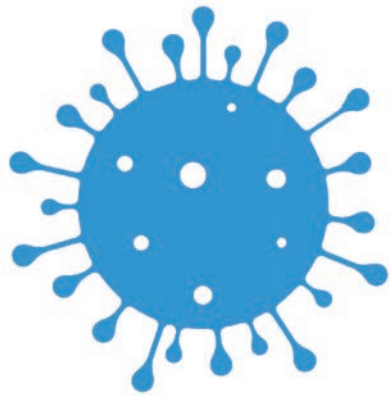

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New SARS-Cov-2 variants identified

By Linda Wilson
Senior Editor

There is an unsettling development in the COVID-19 pandemic – new variants of SARS-CoV-2, the virus that causes the disease.

According to the Centers for Disease Control and Prevention (CDC), at least two new variants are circulating, and they are:

- 20B/501Y.V1, VOC 202012/01, or B.1.1.7 lineage, which emerged in the United Kingdom in September with an unusually large number of mutations, and this variant has been detected around the world, including in the United States and Canada.
- 20C/501Y.V2, or B.1.351 lineage, which emerged in South Africa independently of the B.1.1.7 lineage but shares some mutations with the B.1.1.7 lineage.

In addition to South Africa, where it was identified in October, the variant also materialized in Zambia in late December 2020.

The CDC said that the variant in the United Kingdom, B.1.1.7, is associated with more efficient and rapid transmission than the dominant form of the virus that had been circulating in 2020. Increased transmission can lead to a higher volume of cases, hospitalizations and deaths.

So far, there has not been evidence to suggest that either variant has any impact on disease severity or the efficacy of vaccines, according to the CDC.

The CDC also said that viruses generally mutate over time, leading to new variants, so public health experts were not surprised that this is what happened with SARS-CoV-2. For example, the strain of SARS-CoV-2 that first appeared in China in December 2019 was overtaken by a variant that became the dominant strain throughout the world by April 2020. The CDC also said that SARS-CoV-2 acquires about one new mutation in its genome every two weeks.

The CDC and other public health bodies have taken steps to detect and monitor the presence of new strains of SARS-CoV-2. State and local health departments send out 750 samples per week for sequencing and characterization. Under contract with the CDC, large reference labs also are sending sequencing data to the CDC, while some universities are conducting genomic surveillance.

Meanwhile, the U.S. Food and Drug Administration (FDA) said it is monitoring the potential impact of these viral mutations, particularly B.1.1.7, on authorized SARS-CoV-2 molecular tests. The agency said it is doing so because false negative results can occur with any molecular test if a mutation occurs in the part of SARs-Cov-2's genome assessed by that test.

However, FDA experts also said they believe the risk that these mutations will impact overall testing accuracy is low. CDC officials concur, noting that polymerase chain reaction (PCR) tests for SARS-CoV-2 generally rely on the detection of multiple regions of the genome, so even if one target is impacted, the test should still be able to uncover the other target(s).

The FDA said there are three currently authorized molecular tests – Mesa Biotech Accula, Thermo Fisher TaqPath COVID-19 Combo Kit, and Linea COVID-19 Assay Kit – that may be impacted by genetic variants of SARS-CoV-2, but the impact appears to be insignificant.

What does this mean for laboratorians? It is important to take note of the latest research on SARS-CoV-2 variants, as well as any information that agencies like the FDA or CDC publish on the impact of the variants on commercially available COVID-19 molecular tests. Of course, the FDA also encourages laboratorians to report any issues with these tests to the agency through MedWatch, which is the FDA's safety and adverse-event reporting program.

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

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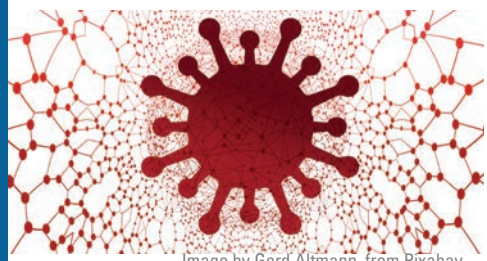


Image by Gerd Altmann from Pixabay

Fast Facts

Household transmission of SARS-CoV-2

The Centers for Disease Control and Prevention measured virus transmission in households with an infected person using RT-PCR testing for 14 days after the index patient's illness onset date.

59 percent
had detectable SARS-CoV-2 at any time.

76 percent
of test results were positive within 7 days.

86 percent
were positive within 10 days.

95 percent
were positive within 14 days.

81 percent
was chance of remaining asymptomatic with negative test results after day 7.

93 percent
was the chance of remaining asymptomatic with negative test results through day 10.

95 percent
was the chance of remaining asymptomatic with negative test results through day 14.

Source: https://www.cdc.gov/mmwr/volumes/69/wr/mm695152a1.htm?s_cid=mm695152a1_w

COVID-19 model compares effectiveness of vaccine and mitigation strategies

Predicting the spread of COVID-19 using standard statistical models has its challenges, which is why two Iowa State University researchers developed a network-based approach to look at the impact of specific policies and vaccination strategies throughout the many stages of the pandemic, according to a press release from the university.

In a paper, published on medRxiv prior to peer review, the researchers used their social-interaction network model to understand how homophily – the tendency to associate with people who share the same opinions and beliefs, in this case about COVID-19 – affects the probability of an outbreak and the number of deaths. The model compares the probability of an outbreak for different levels of homophily and correlations among beliefs about vaccination and social distancing. The researchers kept the same proportion of individuals with positive beliefs in all scenarios to provide an apples-to-apples comparison.

The model showed that the presence of homophily can have a strong influence on the probability of an outbreak. Homophily regarding vaccination implies there are clusters of vaccinated people but also clusters of unvaccinated people. The researchers found that such homophily in social interaction networks can lead to substantially more frequent outbreaks, especially in the presence of an effective vaccine.

They also found outbreaks occurred more frequently when there was a positive correlation between beliefs about vaccination and social distancing. If individuals who get the vaccine are the same people who are more likely to social distance, there is a percentage of the population not taking any protective measures, increasing the risk of an outbreak.

When there is a negative correlation – people get the vaccine, but don't social distance or people social distance, but don't get the vaccine – there are fewer outbreaks, because more people are following one of the mitigation strategies. The researchers said their model provides a more realistic assessment of how our interactions and increasing polarization of opinion impact the spread of the virus.

Study uncovers blood vessel damage and inflammation in COVID-19 patients' brains

In an in-depth study of how COVID-19 affects a patient's brain, researchers at the National Institutes of Health (NIH) consistently spotted hallmarks of damage caused by thinning and leaky brain blood vessels in tissue samples from patients who died shortly after contracting the disease, according to a press release from NIH.

In addition, they saw no signs of SARS-CoV-2 in the tissue samples, suggesting the damage was not caused by a direct viral attack on the brain. The results were published as a correspondence in the *New England Journal of Medicine.*

Although COVID-19 is primarily a respiratory disease, patients often experience neurological problems including headaches, delirium, cognitive dysfunction, dizziness, fatigue, and loss of the sense of smell. The disease may also cause patients to suffer strokes and other neuropathologies.

In this study, the researchers conducted an in-depth examination of brain tissue samples from 19 patients who had died after experiencing COVID-19 between March and July 2020. Samples from 16 of the patients were provided by the Office of the Chief Medical Examiner in New York City while the other 3 cases were provided by the department of pathology at the University of Iowa College of Medicine, Iowa City. The patients died at a wide range of ages, from 5 to 73 years old. They died within a few hours to two months after reporting symptoms. Many patients had one or more risk factors, including diabetes, obesity, and cardiovascular disease. Eight of the patients were found dead at home or in public settings. Another three patients collapsed and died suddenly.

Initially, the researchers used a special, high-powered magnetic resonance imaging (MRI) scanner that is 4 to 10 times more sensitive than most MRI scanners, to examine samples of the olfactory bulbs and brainstems from each patient. These regions are thought to be highly susceptible to COVID-19. Olfactory bulbs control our sense of smell while the brainstem controls our breathing and heart rate. The scans revealed that both regions had an abundance of bright spots, called hyperintensities, that often indicate inflammation, and dark spots, called hypointensities, that represent bleeding.

The researchers then used the scans as a guide to examine the spots more closely under a microscope. They found that the bright spots contained blood vessels that were thinner than normal and sometimes leaking blood proteins, like fibrinogen, into the brain. This appeared to trigger an immune reaction. The spots were surrounded by T cells from the blood and the brain's own immune cells called microglia. In contrast, the dark spots contained both clotted and leaky blood vessels but no immune response.

Questionnaire identifies COVID-19 impact and challenges among healthcare organizations

Healthcare organizations across all settings have faced common challenges during COVID-19, including staffing issues, obtaining supplies, and implementing safety protocols and guidelines, according to a survey conducted by The Joint Commission and reported in a press release.

To learn about the needs of organizations in the current and evolving pandemic environment, The Joint Commission conducted an online questionnaire in September 2020 among healthcare organizations that work with The Joint Commission, Joint Commission Resources, and the Joint Commission Center for Transforming Healthcare.

The questionnaire, administered by C+R Research, had a total of 735 respondents representing a variety of healthcare settings, including hospitals, home care, behavioral health and human services, and ambulatory care.

Most survey participants reported a medium to high impact on their organizations from COVID-19 and often perceived a higher impact than the number of COVID-19 cases in their area may have indicated.

Survey participants said the most common changes resulting from COVID-19 included increased communication to keep staff updated on changes and to support their well-being, increased working-from-home activities and changed plans to deal with staffing shortages. They also said they established and updated protocols, such as for infection prevention and emergency management plans.

When asked about valuable resources, participants pointed to those that helped them monitor changes and adapt their plans accordingly. These included communications on regulatory or guideline changes resulting from COVID-19, information on modifications to infection prevention plans and additional training as governmental recommendations evolved.

Los Alamos study hopes to characterize and optimize ventilator treatment for COVID-19

Cross-disciplinary scientists and engineers at Los Alamos National Laboratory are working to learn how Intrapulmonary Percussive Ventilation (IPV) helps clear mucus from blocking the airways of the human lung, a common reaction to the COVID-19 virus, according to a press release.

Researchers, using some of the same modeling and experimental techniques from the laboratory's nuclear weapons mission, are working to discover the underlying science and engineering principles behind this process and have developed a preliminary machine learning algorithm that could someday assist pulmonary doctors in treating COVID-19 patients with IPV.

IPV is used alongside traditional ventilation to deliver rapid pulses of aerosol, depositing medication and potentially opening up clogged airway passages in the lung. Researchers are merging numerical and experimental approaches to develop a predictive model of lung behavior under these conditions.

The lung is a highly complex system, so the laboratory is using acoustic measurements, computational fluid dynamics models, structural-fluid interaction models, and optical techniques to model the breathing process and observe aerosol flow and mucus breakup. This is especially challenging because of the complex geometries in lung structure, multifaceted boundary conditions in the deep lung, and non-linear behavior of viscus fluids in the lung. The study requires analysis of how the lung responds to the kinetic energy of variable pressures, rotational flows, and sheer stresses on the lung walls.

To inform the mathematical models, the research team designed, built and tested several experimental devices, including a 3D printed "gas distribution manifold" that mimics the structures of the lung's trachea and bronchial branches. They used sensors to measure pressure, velocity, temperature and humidity, along with a gas analyzer to measure pressure and volume, optical sensors to detect aerosol density and spectrometers to look at particle size distribution. They also used lung tissue harvested from sheep carcasses and dyed aerosol to track the deposition of IPV aerosols during a ventilation-assisted process.

The preliminary machine learning algorithm ties all the variables together, with the hope of eventually creating a rapid, patient-specific tool for estimating the proper ventilator and IPV settings for a particular patient before ventilation is begun, responding to and optimizing the treatment for each patient.

CDC reports on allergic reactions to COVID-19 vaccine

During December 14-23, 21 cases of anaphylaxis, a life-threatening allergic reaction, were reported after administration of the first dose of the Pfizer-BioNTech COVID-19 vaccine, or a rate of 11.1 cases per million doses, compared with 1.3 cases per million doses for the flu vaccine, officials from the Centers for Disease Control and Prevention (CDC) reported at a press conference.

The agency also reported on the findings in its Morbidity and Mortality Weekly Report (MMWR).

"The anaphylaxis rate for COVID-19 may seem high compared to flu vaccines, but I want to reassure you this is still a rare outcome," said Nancy Messonnier, MD, Director of CDC's National Center for Immunization and Respiratory Diseases. "That doesn't mean we couldn't see potential serious health events in the future," she added, saying that the CDC and FDA are reviewing all serious adverse event reports.

"I also think it is important to remember that many adverse events following immunization are coincidental," Messonnier said.

The findings were based on the first doses of the vaccine distributed in the United States following the decision by the U.S. Food and Drug Administration (FDA) to issue an emergency use authorization (EUA) for the Pfizer-BioNTech COVID-19 vaccine on December 11, 2020.

The vaccine is administered in two doses separated by 21 days.

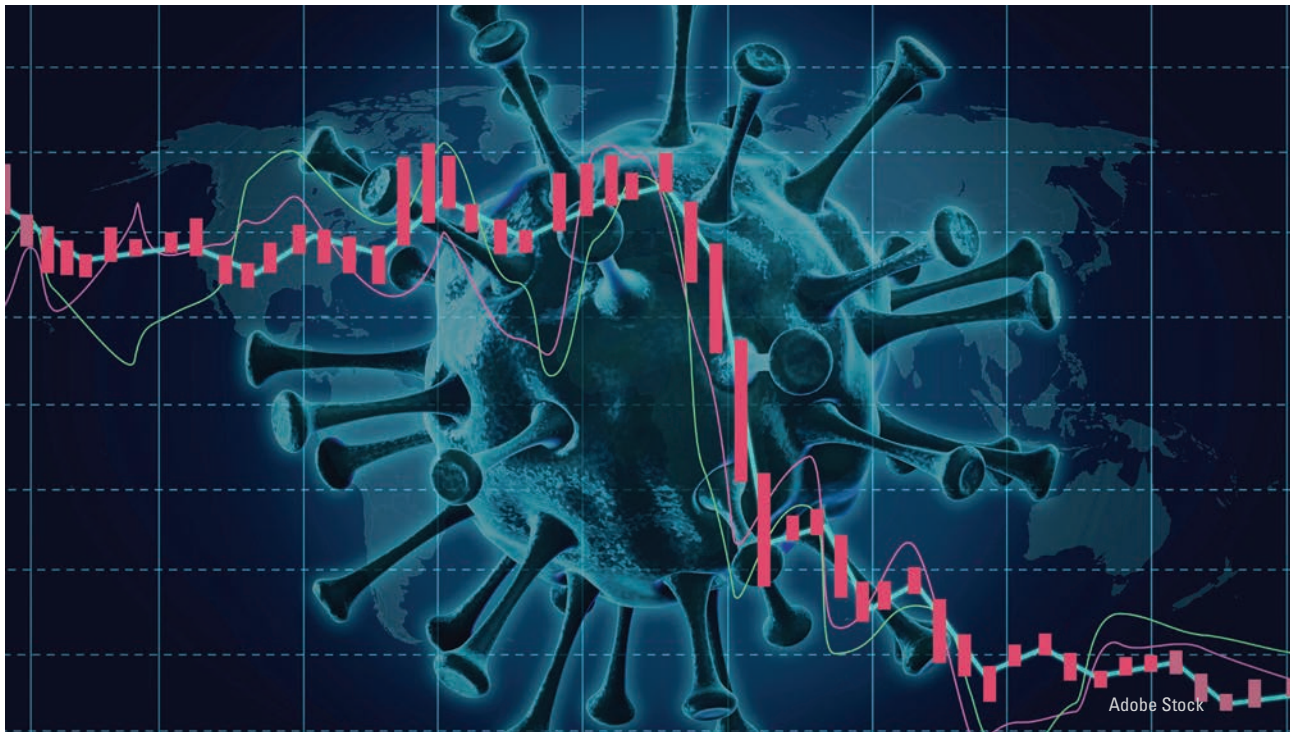
As of December 23, 2020, a total of 1,893,360 first doses of the Pfizer-BioNTech COVID-19 vaccine had been administered in the United States, and reports of 4,393 (0.2 percent) adverse events after receipt of the Pfizer BioNTech COVID-19 vaccine had been submitted to the CDC. Among these, 175 case reports were identified for further review as possible cases of severe allergic reaction.

Based on the data, the CDC said providers should follow the agency's guidelines for COVID-19 vaccine administration for vaccines from both Pfizer-BioNTech and Moderna, which received EUA approval from the FDA for its vaccine on December 18., 2020.

"Locations administering COVID-19 vaccines should adhere to CDC guidance for use of COVID-19 vaccines, including screening recipients for contraindications and precautions, having the necessary supplies available to manage anaphylaxis, implementing the recommended post-vaccination observation periods, and immediately treating suspected cases of anaphylaxis with intramuscular injection of epinephrine," the CDC wrote in the MMWR.

CDC also said that people who had an immediate reaction to the first dose should not get a second dose. Similarly, people who are allergic to any of the components in the vaccines also should not be vaccinated.

CDC officials also said they plan to publish a similar MMWR report on adverse events associated with the Moderna vaccine.



The role of cycle threshold values in infectious disease diagnostics

By Kelly Hughes, PhD, Sonia Rao, PharmD, BCIDP, BCPS, and Davide Manissero, MD, MRCPCH, MSc, DTM&H

Effective interventions in the management of infectious diseases rely on rapid and specific detection of causative pathogens, driving patient care decisions and outcomes. Successful pathogen detection is facilitated by reliable, accurate diagnostic tools; and among the variety of testing tools available, molecular assays such as polymerase chain reaction (PCR) have become dominant. Sensitivity and specificity are paramount in diagnostics and molecular testing provides both. In theory, PCR can detect the presence of a single copy of nucleic acid from a single organism. The use of sequence-specific primers and probes in these assays yields unparalleled specificity and allows for testing to be multiplexed to detect multiple pathogens in one test run. This specificity allows not only for detection, but also for determining the presence of specific genes for typing different strains and antimicrobial resistance profiling.[1] Alternatively, primers and probes can be designed to be less specific, or target highly conserved regions, to provide broad coverage and detect divergent pathogen genomes.[2]

PCR testing is successful in identifying organisms that cannot be grown *in vitro* or in situations where current culturing techniques lack sensitivity and/or require prolonged incubation periods.[2] Other testing methods, such as culture or serology, often do not match the level of sensitivity or timeliness of molecular testing. In some cases, alternative methods may increase the risk of false negatives or incorrect results in critical testing situations where fastidious pathogens may be difficult to grow or immune responses difficult to detect.

Utility of cycle threshold values

Effective PCR tests have now been developed for a wide variety of pathogens. However, these PCR tests, specifically real-time PCR (RT-PCR) tests, can reveal more than just the simple presence of a pathogen. Results from molecular tests are typically reported in a binary, positive or negative manner; however, this approach may not recognize the full benefits these assays have to offer. In addition to reporting pathogen detection, RT-PCR reports cycle threshold (Ct) values. The cycle threshold is defined as the thermal cycle number at which the fluorescent signal exceeds that of the background and, therefore, passes the threshold for positivity. Ct value is inversely related to the quantity of target nucleic acid in the sample, with lower Ct values reflecting higher viral loads, which

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LEARNING OBJECTIVES

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

1. Recall the strengths and limitations of RT-PCR tests.
2. Describe the definition of cycle threshold (Ct) value and how it is used in infectious disease diagnostics.
3. Discuss research into the utility of Ct values in assessing COVID-19 disease progression.
4. Discuss research into the utility of Ct values in assessing disease progression for other respiratory diseases as well as gastrointestinal illnesses.

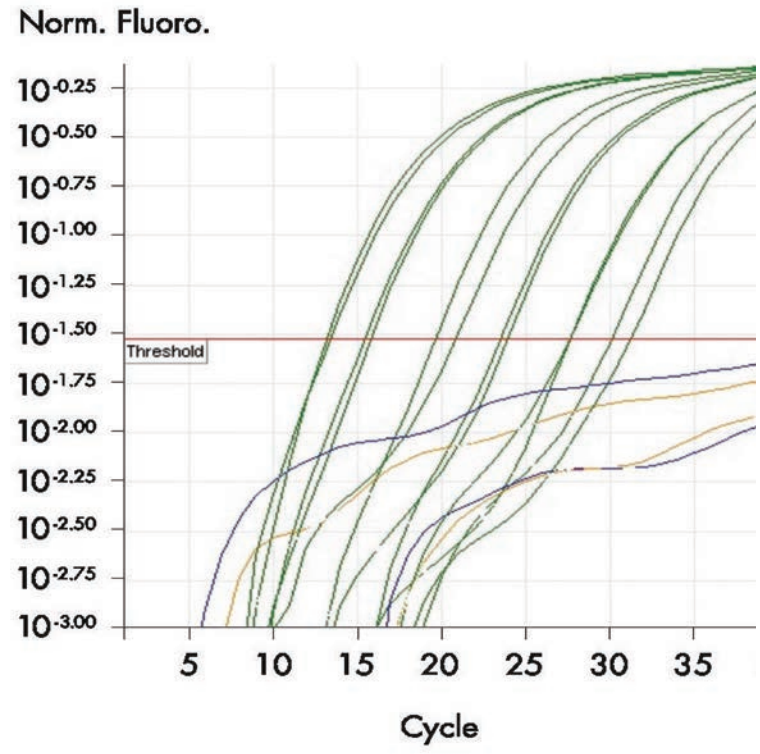
can allow for comparison of relative levels of pathogen. Using this principle, a more specific quantification may be obtained with the use of a standard curve of known DNA quantity. This quantification can help establish pathogen burden and distinguish between what are normal, commensal levels and what are pathogenic levels of a microbe.

In addition to quantification, Ct values can provide additional information that may be useful when complex or unexpected results are received. Analysis of amplification curves and Ct values can be helpful in assessing sample quality and/or potential contamination. For patients with co-infections, the Ct values from a multiplex panel can help clarify which pathogen is most likely the causative agent in an illness. For patients on antimicrobial therapy, comparison of Ct values over time can be used as an indicator of the response to therapy.[1]

While PCR testing and Ct values can offer a deeper insight during the diagnostic process, they are not without limitations; perhaps the most important of which is the inherent inability to distinguish between live and dead organisms. The exquisite sensitivity of PCR allows for the detection of minute quantities of nucleic acid; however, this does not always correlate with the presence of live organisms. The assay will amplify nucleic acid from dead microbes as readily as from living.[1] As dead organisms can be shed for weeks after recovery, a recovering patient might have the same positive test result as an actively infected patient. It is important to be able to distinguish between these two patients, as the positive test from the recovering patient may have no clinical relevance, while the actively infected patient may require treatment. In this situation, utilizing Ct values for relative quantification of the pathogen may help the clinician distinguish between these two patients.[3]

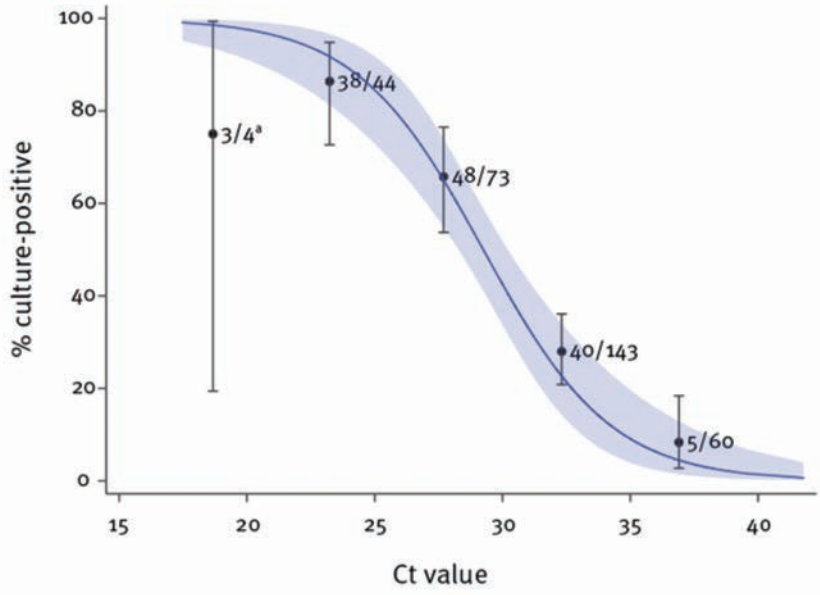
It is important to understand that Ct values should not be interpreted as a unit of pathogen load without a standard curve. This is due to the number of variables that can affect reaction efficiency and amplification. As a result, Ct values are dependent on multiple factors, including sample type and quality. For example, the presence of inhibitory factors in a sample will reduce reaction efficiency, affecting both Ct values and final test results. Inconsistencies between different assays and machines must also be taken into consideration. Without a standard curve, Ct values can still provide an indirect, relative quantification of pathogen load; however, it is important to keep in mind that Ct values can only be compared if the reaction efficiency is

Figure 1. RT-PCR Amplification plot



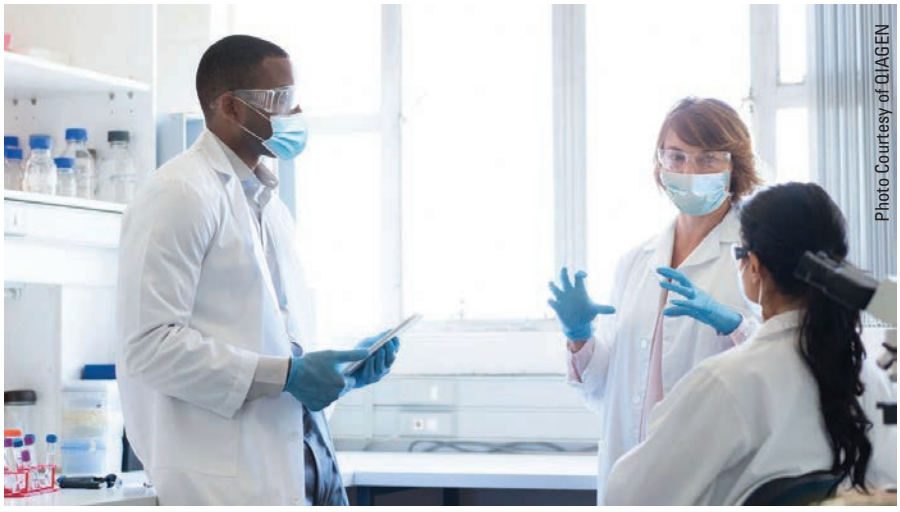
Amplification plot from RT-PCR assay, showing positive samples (green) with threshold used to determine Ct values, and negative samples (purple, yellow) Source: QIAGEN

Figure 2. Ct value is strongly related to the ability to recover infectious SARS-CoV-2 virus



The ability to recover infectious virus is strongly related to Ct value, as the estimated odds ratio of finding infectious SARS-CoV-2 virus decrease by 0.67 for every unit increase in Ct value. All five samples with Ct >35 from which virus was successfully propagated were from symptomatic patients and none had severe illness. Source: Centers for Disease Control and Prevention. Wide confidence levels is due to small sample size. https://www.cdc.gov/library/covid19/090420_covidupdate.html source:covid19/090420_covidupdate.html

Ct values can inform patient management



The additional information provided by Ct values can help clinicians determine the best course of action in patient management.

similar and the target genes have the same number of copies.[4] This additional layer of complexity in understanding Ct values may limit a broader use of this data, narrowing use to only those personnel who have been trained to understand and appropriately interpret data from RT-PCR tests.

Ct values in COVID-19

The ongoing COVID-19 pandemic, with its clinical unknowns and a lack of standardized quantitative assays for Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), has brought on an unprecedented level of interest in the clinical utility of Ct values. Patients infected with SARS-CoV-2 can display an array of clinical presentations, ranging from an absence of symptoms, to the requirement of intensive care and respiratory support, to an eventually fatal outcome.[5]

In fact, the proposed disease pathogenesis of COVID-19 indicates two overlapping disease states: an initial viremic phase where signs and symptoms are attributable to viral replication, and a subsequent inflammatory phase where the severity and critical illness is attributable to a "cytokine storm."[6] While these two phases have different management implications from a treatment choice perspective – antiviral/antibody therapy versus anti-inflammatory therapy – a clear prognostic approach is still missing. The ability to predict prognosis and infectiousness of patients during the viraemic phase could fundamentally impact triage and management of patients and, potentially, of their contacts.

Early in the COVID-19 pandemic it was suggested that evidence from the 2002 SARS-CoV epidemic indicated that higher viral loads were associated with increased need for intensive care and overall worse outcomes. While there are differences between SARS-CoV and SARS-CoV-2, it has emerged that, similar to SARS-CoV, the viral load of SARS-CoV-2 could also play a key role in determining COVID-19 disease severity and prognosis, as well as infectiousness.[3,7-11]

While the recent appearance of antigen tests has added to the panel of diagnostic solutions for COVID-19, RT-PCR has been the gold standard diagnostic approach since the beginning of the pandemic. Several of the COVID-19 RT-PCR solutions available on the market provide Ct values as part of their results data, and experts argue that these could be used as a semi-quantitative proxy for viral load in the absence of quantitative assays.

A recent systematic review assessed evidence to establish whether SARS-CoV-2 Ct values correlate with clinical outcomes and, therefore, whether they could provide valuable patient management information to clinicans.[12] The findings indicate that lower Ct values may be associated with adverse outcomes and, in several instances, a correlation with clinical course and prognosis was identified. While the review concluded that, in general, higher Ct values correlate with lower viral loads, limitations have been highlighted around the fact that Ct values and lower viral load may not be directly proportional due to the presence of inhibitory factors within samples as well as the linear dynamic range of the assay.[4]

While the results of SARS-CoV-2 PCR diagnostic assays remain – in the majority of cases – reported as positive or negative results in the clinical setting, a discussion has emerged about the possibility of reporting and interpreting Ct values to aid clinicians in patient management. The increasing evidence supporting the utility of Ct values has led public health authorities, such as Public Health England and the Centers for Disease Control and Prevention (CDC), to develop guidance and recommendations regarding their use. Experts agree that if Ct values are to be reported, linearity, limits of detection and reference quantification curves must be standardized and validated. Interpretations of a single positive Ct value may be of limited use in the clinic.[13,14] However, indications are emerging that serial Ct values may offer greater utility for the purpose of clinical management.[13]

What is certain is that – in the absence of quantitative assays for SARS-CoV-2 – Ct values have become of increasing interest with regard to providing interpretative guidance, including as a potential benchmark for the development of antigen and rapid tests.

Ct values beyond COVID-19

With, finally, a light at the end of the tunnel with the emergency use authorization (EUA) of several COVID-19 vaccines, it would be remiss not to highlight the potential application of Ct values beyond SARS-CoV-2. Prior to the COVID-19 pandemic, the most common causes of respiratory illness in seasonal circulation were influenza virus, respiratory syncytial virus (RSV), parainfluenza virus (PiV), human metapneumovirus (HMPV), adenovirus (AdV), rhinovirus and coronavirus (hCoV). RT-PCR is one of the most common diagnostic modalities for detection and identification of respiratory pathogens. There are several studies that have attempted to elucidate the clinical utility of Ct values for respiratory pathogens with contradictory reports that Ct values are associated with disease severity, intensive care unit (ICU) admission and length of hospital stay (LOS).[15-17]

The results of many studies evaluating associations between Ct values and clinical outcomes for patients with influenza were conflicting. However, a large influenza study identified that patients with low Ct values were significantly more likely to self-report moderate to high disease severity and fever.[18] Several studies of patients with RSV reported association between low Ct values with clinically meaningful outcomes such as hospitalization, radiographical evidence of pneumonia or LOS, while others have failed to identify such associations. Despite many small rhinovirus studies having no association between Ct values and patient

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outcomes, there are a few large studies that found that low Ct values were associated with symptom severity and hospital LOS.[19] For non-SARS-CoV-2 respiratory pathogens, Ct values for some respiratory infections may be useful in guiding treatment and healthcare decisions; however, the evidence supporting utility of Ct values is conflicting and warrants further investigation.

Multiplex PCR testing for viral, bacterial, and parasitic causes of gastrointestinal illnesses is one of the newer uses of syndromic diagnostic testing. As infectious diarrhea is estimated to cause more than 48 million illnesses and 3,000 deaths per year in the United States alone, any markers that could potentially help stratify patients to aid in clinical management is greatly needed. Compared to respiratory illness, there are fewer studies investigating a correlation of Ct values and clinical outcomes for gastrointestinal pathogens. A case-control study evaluated the application of molecular detection on relative amounts of gastrointestinal pathogens.[20] There were significantly higher pathogen loads in cases versus controls for *Campylobacter spp*., *Salmonella spp*. Enterotoxigenic *Escherichia coli* (ETEC), typical Enteropathogenic *E. Coli* (EPEC) and *C. parvus/hominis*. Of note, Ct values for *C. difficile* and Enteroaggregative E.Coli (EAEC) were significantly lower for cases than for controls in patients 21–50 years old, and Ct values for atypical EPEC were significantly lower in cases than control for patients younger than 5 years old.

This study highlighted that low Ct values indicate high pathogen load and have the potential to suggest microbiological causes of gastroenteritis. A separate study specifically assessed the utility of Ct values on *C. difficile* disease and found significantly lower Ct values reported for patients with severe disease versus those with mild/moderate disease (median Ct values 25.9 vs 28.1, respectively; p=0.00001), with significant difference in the median age between samples with Ct values <25 and Ct values >25 , 79 and 74 years, respectively (p=0.004).[21]

As treatment of *C. difficile* infections is guided by severity of symptoms and disease, the ability to predict severity of disease through Ct values as a surrogate for bacterial load has the potential to impact patient management and antimicrobial selection.

Conclusion

In conclusion, there are many considerations when utilizing Ct values as a surrogate for pathogen load in the laboratory setting and for use in the patient management decisions. However, the COVID-19 pandemic has highlighted the potential ability of Ct values to assess disease severity and those at higher risk of mortality. Although for other infectious pathogens the evidence is not as conclusive and many studies are conflicting, we should continue to evaluate the utility of Ct values to determine impact on patient management, as well as educate both laboratorians and clinicians on how to best interpret this numerical degree of PCR test positivity.

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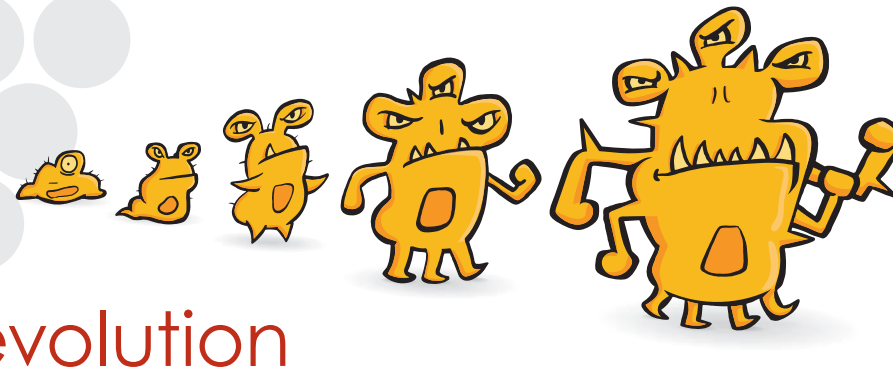

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1. **Among the variety of testing tools available, molecular assays such as____ have become dominant.**
   - A. next generation sequencing
   - B. polymerase chain reaction (PCR)
   - C. flow cytometry
   - D. genomic testing

2. **The use of sequence specific primers and probes in PCR assays yields unparalleled specificity and allows for testing to be multiplexed to detect multiple pathogens in one test run.**
   - A. True
   - B. False

3. **PCR testing can verify the presence of specific genes, enabling laboratorians to:**
   - A. type different strains of disease; determine appropriate pharmacologic agents
   - B. complete antimicrobial resistance profiling; determine if the virus is active
   - C. type different strains of disease; complete antimicrobial resistance profiling
   - D. determine if the virus is active; complete antimicrobial resistance profiling

4. **PCR testing might be a good choice in situations in which current culturing techniques:**
   - A. lack sensitivity and/or require prolonged incubation periods
   - B. are not able to recognize viable cells and/or require highly skilled personnel
   - C. are very sensitive and/or resource intensive
   - D. are resource intensive and/or require highly skilled personnel

5. **In addition to reporting pathogen detection, RT-PCR reports____.**
   - A. cycle threshold values
   - B. complete blood count
   - C. activity levels of proteins
   - D. whole chromosomes

6. **The cycle threshold is defined as the thermal cycle number at which the fluorescent signal exceeds that of the ____ and, therefore, passes the threshold for ____.**
   - A. foreground; negativity
   - B. background; negativity
   - C. foreground; positivity
   - D. background; positivity

7. **Ct value is ____related to pathogen quantity, with lower Ct values reflecting ____ viral loads, which can allow for comparison of relative levels of pathogen.**
   - A. inversely; lower
   - B. inversely; higher
   - C. directly; lower
   - D. directly; higher

8. **A quantification obtained with the use of a standard curve of known ____ can help establish pathogen burden and distinguish between what are ____, commensal levels and what are pathogenic levels of a microbe.**
   - A. DNA quantity; normal
   - B. RNA quantity; abnormal
   - C. DNA quantity; abnormal
   - D. RNA quantity; normal

9. **For patients with co-infections, the Ct values from a multiplex panel can help clarify which pathogen is most likely the causative agent in an illness.**
   - A. True
   - B. False

10. **One limitation of PCR testing is its inherent inability to:**
    - A. quantify nucleic acid
    - B. distinguish between live and dead organisms
    - C. produce high false positive results
    - D. produce high false negative results

11. **The presence of inhibitory factors in a sample will reduce reaction ____, affecting both Ct values and final test results.**
    - A. time
    - B. specificity
    - C. efficiency
    - D. inefficiency

12. **It is important to keep in mind that Ct values can only be compared if the reaction efficiency is similar and the target ____have the same number of copies.**
    - A. nucleic acids
    - B. genes
    - C. chromosomes
    - D. proteins

13. **The ongoing COVID-19 pandemic has brought on an unprecedented level of interest in the clinical utility of Ct values because of the ____.**
    - A. clinical unknowns of the virus
    - B. lack of standardized quantitative assays for SARS-CoV-2
    - C. lack of treatments
    - D. A and B

14. **There are no COIVD-19 RT-PRC solutions available on the market that provide Ct values as part of their results data.**
    - A. True
    - B. False

15. **If Ct values are to be reported, ____, ____ and reference quantification curves must be standardized and validated.**
    - A. regression, linearity
    - B. linearity; limits of detection
    - C. limits of detection, regression
    - D. linearity; analytical sensitivity

16. **Indications are emerging that serial Ct values may offer greater utility for the purpose of clinical management of ____.**
    - A. SARS-CoV-2
    - B. influenza
    - C. respiratory syncytial virus
    - D. adenovirus

17. **A large influenza study identified that patients with ____ Ct values were significantly more likely to self-report ____ disease severity and fever.**
    - A. low; low to moderate
    - B. high; low to moderate
    - C. low; moderate to high
    - D. high; moderate to high

18. **Multiplex PCR testing for viral, bacterial, and parasitic causes of ____ illnesses is one of the newer uses of syndromic diagnostic testing.**
    - A. neurological
    - B. gastrointestinal
    - C. respiratory
    - D. circulatory

19. **Infectious diarrhea is estimated to cause more than ____ million illnesses and 3,000 deaths per year in the United States.**
    - A. 18
    - B. 25
    - C. 48
    - D. 59

20. **One study highlighted that ____Ct values indicate ____ pathogen load and have the potential to suggest microbiological causes of gastroenteritis.**
    - A. low; high
    - B. high; low
    - C. low; low
    - D. high; high

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SARS-CoV-2 and vascular and multi-system dysfunction

By Martin Conway, BSc

COVID-19, the disease caused by SARS-CoV-2, will present in many patients as a minor cold or flu, however, those with health complications – such as autoimmune diseases, asthma, heart disease and diabetes – are at greater risk of developing serious illness and adverse outcomes. And as many as 1 out of 6 patients will experience complications that could be life-threatening.

SARS-CoV-2 is thought to be a respiratory virus, primarily targeting pulmonary tissue. However, experts now agree that the virus attacks multiple critical organs and cell types including the cardiovascular system and vascular endothelial cells.

Potential therapies that address vascular system dysfunction and its sequela may have an important role in treating SARS-CoV-2 infection and its long-lasting effects. The endothelium maintains homeostasis through regulation of immune competence, inflammatory equilibrium, tight junctional barriers, hemodynamic stability, as well as optimally balanced thrombotic and fibrinolytic pathways. The novel coronavirus causes dysregulation of many of these pathways and has emerged as a mediator of severe disease.

Clinical and biomarker findings have identified how SARS-CoV-2 disrupts the immune, renin-angiotesin-aldosterone and thrombolytic balance, which are common pathways on the vascular endothelium. There are still a lot of unknowns about the novel coronavirus (SARS-CoV-2), with current knowledge mostly based on what the industry has learned about existing coronaviruses including MERS-CoV and SARS-CoV.[1]

After viral genome analysis, the coronavirus study group (CSG) of the International Committee on Taxonomy of Viruses concluded that the virus shares 88 percent of its genetic code with two bat-derived severe acute respiratory syndrome (SARS-like) coronaviruses. However, the study group also concluded that the sequence was more distant from SARS-CoV.[2] The spikes crowning SARS-CoV-2 are typical of pneumonia in how they attach, fuse and gain entry to cells.[3] Furthermore, this essentially interrupts the vascular endothelium, impacting a patient's inflammatory response, and progressing to further complications linked to induced end-organ dysfunction such as cardiovascular disease, ARDS, vasoplegia and immune exhaustion. (**See Figure 1**)

As the spread and devastation of the COVID-19 pandemic continues to grow, laboratory testing plays an essential role in both diagnosis and management of patients with COVID-19. Consequently, it is vital that fast and accurate diagnostic testing strategies are implemented for effective risk stratification, monitoring of treatment efficacy and recovery.

Vascular abnormalities – dysregulation, endothelial injury and cytokine storm

The vascular endothelium plays a role in immune regulation and inflammation in which SARS-CoV-2 infection interrupts. Studies surrounding inflammation in patients with COVID-19 have strong links to cytokine storms, macrophage activating syndrome and subsequent immune exhaustion. [4]

Cytokines have a vital role in the immune system and are known to be involved in the body's response to a variety of inflammatory and infectious diseases. Overstimulation of cytokines in response to infection is known as a "cytokine storm," a common complication of SARS-CoV-2, which strongly correlates with poor disease outcomes, including pneumonitis, acute respiratory distress syndrome (ARDS), shock, multiple organ failure, and potentially death. Many researchers have highlighted the need to identify cytokines, cytokine receptors and growth factors to classify complications where viral replication and excessive, uncontrolled systematic inflammation may lead to further complications.

The overlap in secreted cytokines in response to SARS-CoV-2 and influenza can be explained by the presence of viral RNA in the host cell's cytoplasm during the replication cycle of both viruses, which likely induces the activation of similar intracellular anti-viral pathways and subsequent recruitment of similar immune cells to the respiratory epithelium. SARS-CoV-2's pro-inflammatory immune signature has been likened to macrophage-activation syndrome (MAS), a life-threatening clinical entity observed in autoimmune diseases and mimicked in many viral infections, including influenza. [5]

According to research estimates, 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. 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 approach to treatment.

Using influenza's associated cytokine storm to derive conclusions about COVID-19's potential virulence mechanisms poses challenges for the diagnostics industry because of SARS-CoV-2's expanded tropism. Analysis of the medical data on patients who succumbed to COVID-19 suggest that SARS-CoV-2 infects endothelial cells to cause inflammation. Moreover, viral cytotoxicity could be playing a larger role in mediating severe COVID-19 than in influenza.

Many researchers have said this explains multi-system system organ failure and a hypercoagulable state associated with severe COVID-19, since local pulmonary endothelialitis would result in activation of the coagulation cascade and exuberant production of endothelium-derived pro-inflammatory cytokines without the need to invoke a MAS-like pathologic state. A recent study highlighted that plasma IL-6 levels in COVID-19 patients appear to be significantly lower on average (10- to 40-fold) when compared with those reported in other non-COVID-19 ARDS cohorts that display signs of a cytokine storm. These observations run counter to the hypothesis that elevated serum cytokines are driving the unprecedented morbidity and mortality observed in severe COVID-19, suggesting instead that they are consequences of local vasculopathy. [6]

Associated complications – multi-system dysfunction

The SARS-CoV-2 infection has elicited a swift response by the scientific community to elucidate the pathogenesis in order to develop much needed effective therapeutics. Clinical data indicate that severe COVID-19 most commonly manifests as viral pneumonia-induced acute respiratory distress syndrome (ARDS), a clinical entity mechanistically understood best in the context of influenza A virus-induced pneumonia. Like influenza, advanced age has emerged as the leading risk factor for developing severe COVID-19.

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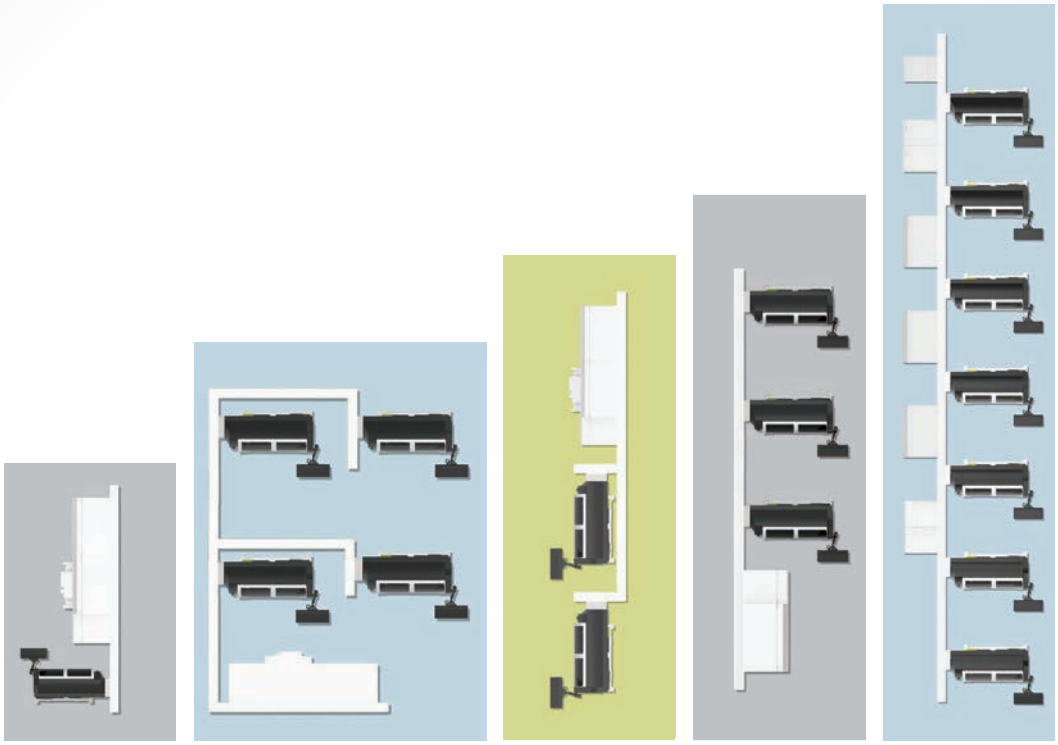

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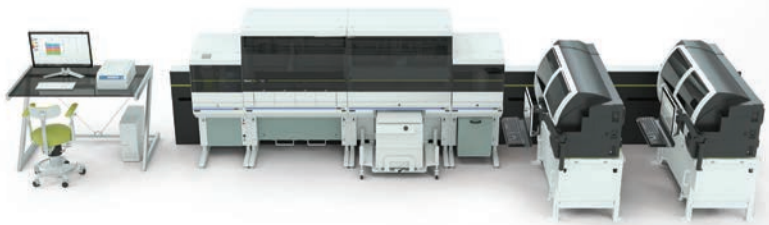

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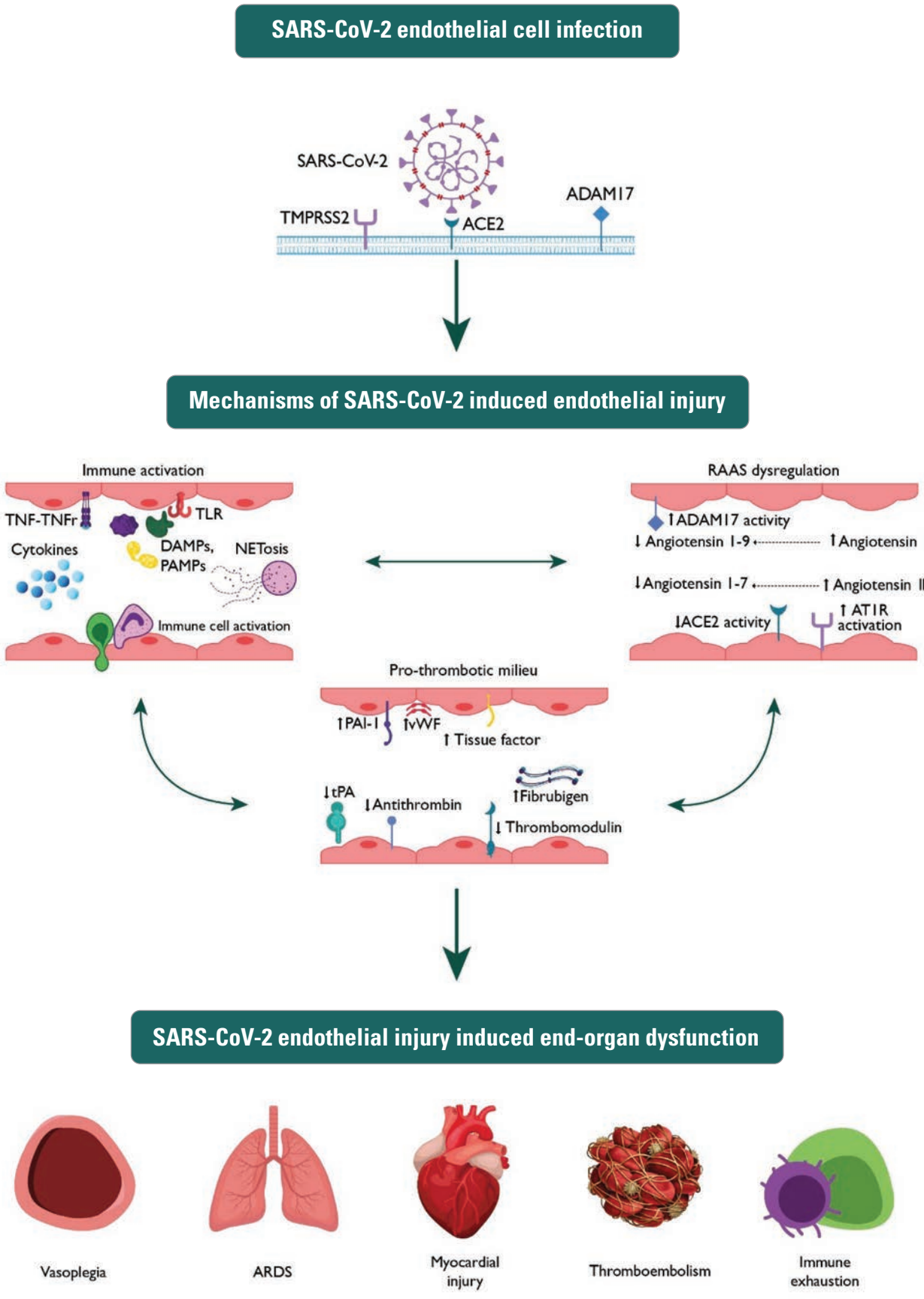
Figure 1: SARS-CoV-2-Induced Endothelial Injury
A schematic of SARS-CoV-2 infection and proposed resulting endothelial injury. These insults interact with each other to cause end-organ dysfunction that is manifest in many COVID-19 patients.



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SARS-CoV-2 identified in most COVID-19 patients with underlying conditions are at a greater risk of experiencing complications that could potentially be life-threatening as they have a greater risk of developing serious illness and adverse complications.

Those illnesses and complications include ARDS, liver damage, acute kidney injury and cardiovascular issues.

Acute respiratory disease syndrome (ARDS)

Most morbidity and mortality related to COVID-19 occurs in the inflammatory phase, characterized by a dysregulated immune response and hypercoagulable state that is associated with life-threatening complications, including cardiac and renal failure, cerebrovascular disease, and ARDS.[7] Strongly linked to vascular abnormalities, ARDS has widely been characterized as a noncardiogenic circulatory disorder of the lungs associated with critical illnesses such as sepsis, trauma, and immune and collagen vascular disease. The demise occurs due to progressive pulmonary hypoxia and multi-organ dysfunction syndrome (MODS) with severe inflammation.[8]

Much progress has been made in understanding the pathophysiology of viral pneumonia induced ARDS, particularly in the context of influenza. However, taking into context the nature of the SARS-CoV-2 virus, common links can be identified. The heterogeneity associated with COVID-19's clinical presentation has prompted the conceptualization of novel paradigms of respiratory disease to explain the observed variability and individualize clinical management of COVID-19.[9]

Hepatic function

Liver damage in patients with coronavirus infections might be directly caused by the viral infection of liver cells. Patients with abnormal liver function tests are at a significantly higher risk of developing severe disease. Significantly elevated bilirubin levels, three times the upper limit, have been observed in COVID-19 patients. Other liver function markers are known to be elevated in COVID-19 patients including both AST and ALT, with markers like Albumin decreased. The presence of ACE2 receptors in the liver taken together with the local effects of systemic inflammation and possible iatrogenic toxicity seem to be the main mechanisms involved in the onset of liver damage in COVID-19 patients.[10]

Researchers have noted that through clinical trials and studies, SARS-CoV-2 has a negative effect on hepatic cells and is associated with other multi-organ failures. In particular, during COVID-19 progression, the liver could be involved either as a direct target of the SARS-CoV-2 (e.g. hepatocyte apoptosis or caspase-dependent pathways) and secondary to the complex pathways of systemic alterations promoted by the viral infection, mainly including inflammation and cytokine release (including IL-1, IL-6, IL-10, immune response, altered coagulation, hepatic ischemia and hypoxia, and sepsis-related abnormalities.

Renal function

The United Kingdom's National Institute for Health and Care Excellence (NICE) recommends that 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.

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. While the Jaffe method is less expensive, it is more susceptible to interferences. These interferences can lead to the misdiagnosis of patients. Moreover, the sensitivity of SCr in the early detection of renal disease is poor, with SCr insensitive to small changes in GFR. Up to 50 percent of renal function can be lost before significant SCr levels become detectable. 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.

Although Cystatin C is a superior marker of renal impairment, employing a multi-marker approach could identify kidney disease or injury at a much earlier stage. Using current technologies, kidney 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.

Cardiovascular function – the importance of Lp(a) testing

SARS-CoV-2 infection also can lead to cardiovascular manifestations in COVID-19 patients, mainly due to the interaction between the viral spike (S) protein and angiotensin-converting enzyme 2, which triggers entry of the virus into host cells. The presence of underlying cardiovascular comorbidities in patients with COVID-19 is associated with high mortality. COVID-19 can cause cardiovascular disorders, including myocardial injury, arrhythmias, acute coronary syndrome and venous thromboembolism. Many patients who present with COVID-19 have increased fibrinogen, fibrin degradation products, D-dimer and von Willebrand factor, and these elevations appear to correlate with severity of disease and thrombotic risk. Earlier reports and findings show a substantial burden of myocardial injury in patients who were critically ill or died from COVID-19.

While infection and hemodynamic stresses of acute critical illness can trigger plaque rupture and result in myocardial infarction, recent reports indicate that some COVID-19 patients show biomarker and electrocardiographic findings of myocardial infarction without evidence of acute plaque rupture on angiography. Furthermore, a recent case series reported a 78 percent prevalence of cardiovascular involvement and myocardial inflammation without apparent left ventricular impairment on cardiac magnetic resonance imaging studies of recovered COVID-19 patients without cardiac symptoms post-discharge from the hospital. This pattern of cardiac injury could result from endothelial dysfunction and coronary microvascular thrombosis in these patients, rather than coronary macrovascular thrombosis. [11]

Lipoprotein(a) / Lp(a) is a strong independent marker of coronary heart-disease risk in patients with heterozygous familial hypercholesterolemia (HeFH). Lp(a) 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.

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Martin Conway, BSc, is a marketing team lead at Randox Laboratories.

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Ionized Magnesium, Not Total, is a Better Indicator of Hypomagnesemia in Renal Replacement Therapy

Hypomagnesemia is common in critically ill patients undergoing renal replacement therapy (RRT) and is associated with increased risk of mortality. Measurement of total plasma magnesium (tMg) is the current clinical practice to assess hypomagnesemia in these patients. However, tMg does not accurately represent the level of ionized magnesium (iMg), the physiologically active fraction of magnesium in blood. Multiple reasons that favor iMg and not tMg in assessing RRT-related hypomagnesemia will be discussed.

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Primary Presenter

Wouter Tiel Groenestege, PhD
Clinical Chemist, Central Diagnostic Laboratory,
University Medical Center, Utrecht, Netherlands

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New tests promise to improve sepsis diagnosis and treatment

By Sherry Dunbar, MBA, PhD

As clinical laboratories know too well, sepsis testing is all about getting accurate, actionable results as quickly as possible to facilitate treatment selection or enable de-escalation for optimal patient outcomes. After all, sepsis represents the ultimate clinical ticking clock – given that patient mortality rates increase nearly 8 percent for each hour that appropriate treatment is delayed.[1]

Years ago, testing options for patients suspected of having bloodstream infections were limited to culture-based workflows, which take several days to deliver final results. Factor in the increasing importance of antibiotic susceptibility testing and suddenly, the timeline for getting high-quality results becomes virtually useless for getting patients on the optimal therapy.

A rapid, molecular blood-culture panel allows clinicians to optimize sepsis therapies more quickly than is possible with a culture-based method alone.

Fortunately, recent advances in testing options – as well as some tests that may be on the horizon – are giving clinical labs critical new tools to diagnose patients suspected of having sepsis. The opportunities in phenotypic and genotypic testing, as well as the shortened turnaround times for results, have dramatically altered the diagnostic landscape for sepsis cases. Together, these improvements are giving physicians actionable information faster than ever and ushering in better prospects for patients with bloodstream infections.

Stages of sepsis

While sepsis can very quickly lead to death, it does follow a clear progression. Along that path, there are several points where it is now possible to intervene with testing to support better clinical decision-making.

The earliest stage occurs prior to sepsis with the precipitating infection, which ultimately triggers the out-of-control immune response that causes sepsis. Ideally, molecular diagnostics or even traditional culture-based microbiology testing would be deployed at this point to identify the pathogen and guide treatment selection in the hopes of helping to reduce the possibility that the patient's immune system overreacts. Unfortunately, this is often not possible, as many patients are not in a healthcare facility at the time of infection, or do not know that their symptoms require a trip to the doctor's office for testing.

As the patient's immune system goes into overdrive responding to the infection, the next stage is sepsis, which is typically characterized by a fever and fast heart or breathing rates. Because these symptoms overlap with so many other health conditions, it is impossible to confirm a suspected diagnosis of sepsis without a lab test. Culture-based tests offered at this stage can yield that answer, but their results take too long to guide targeted treatment decisions in a timely manner. Newer testing options based not on identifying a causal pathogen, but rather on detecting proteins indicative of an overactive immune response, can deliver essential information in the earliest phases of sepsis. The most useful of these tests gives a quick yes-or-no answer, enabling a triage decision about whether the patient should be started on standard sepsis treatments.

After the onset of sepsis, patients may progress into severe sepsis. This phase is marked by organ failure and may feature decreased urination, skin discoloration, low platelet counts, and/or abnormal heart activity, among other symptoms. If severe sepsis has occurred because the standard antibiotic treatments used for sepsis have not worked, it may be an indication that the underlying infection is resistant to those particular therapies. At this stage, gleaning insight into the pathogen's drug-resistance profile is imperative for pinpointing treatments that may be more effective. Genotypic molecular tests can produce this information far more quickly than culture-based susceptibility testing and can be deployed at this point – if not sooner – as physicians seek a more comprehensive view of the patient's situation.

The final stage of the sepsis progression is septic shock, recognizable by extremely low blood pressure that cannot be brought back to normal ranges with medication. In this stage, mortality rates climb to 40 percent, and patients who survive septic shock may develop lifelong complications from blood clots and other problems.[2] In this phase, assuming all relevant laboratory testing has been performed, physicians may reflex to guidelines that do not require lab testing, such

Education references continued from page 20

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as quick sequential organ failure assessment (better known as qSOFA), to help determine the next steps in patient care.

Testing options for sepsis

Recent innovations in diagnostic testing have paved the way for a number of new test options for patients whose symptoms are consistent with sepsis.

There is much excitement around efforts to develop a sepsis triage test that could be used at the earliest signs of illness to determine whether a patient is experiencing sepsis or not. At this stage, identification of the pathogen or drug-resistance markers is less important than getting a simple yes-or-no that would allow physicians to begin standard sepsis treatment. Promising tests in this category are typically based on host protein biomarkers such as lactate, IL-6, procalcitonin, and C-reactive protein, and offer a quick snapshot of the patient's immune state. Triage tests are also being designed based on mRNA panels that may deliver not just a positive or negative result for sepsis but can also determine whether the underlying infection is bacterial or viral.[3]

Any of these tests would rely heavily on multiplexing, as evidence suggests that no single protein or mRNA would be sufficient to provide clinically useful information. Whether assays become available as in vitro diagnostics based on proprietary platforms or as laboratory-developed tests, clinical labs should anticipate running them using multiplex assay technology. This approach would provide the most information possible in the shortest period of time without requiring large sample volumes.

For more detailed information following this kind of broad triage test, rapid molecular diagnostics could identify the causal pathogen and also reveal key elements indicative of drug resistance in just a few hours. These molecular assays are generally available as syndromic panels, detecting a dozen or so of the most common bloodstream infection pathogens. Some assays are also designed to detect key markers of antibiotic resistance. Molecular assays are by nature genotypic instead of phenotypic, so some labs choose to follow up these rapid results with culture-based identification and susceptibility testing for phenotypic confirmation of the results.

An important advantage of using rapid molecular assays for patients believed to have sepsis is the ability to escalate or de-escalate treatment based on these more comprehensive results. Patients who were started on standard broad-spectrum antibiotics, for instance, may be safely shifted to a more targeted treatment, or a treatment that matches the pathogen's drug-resistance profile. This approach promises better outcomes that align with antimicrobial stewardship strategies.

The ideal approach to sepsis testing is to deploy a combination of these tests. For example, pairing a simple triage test – whether that's a point-of-care test based on host protein biomarkers or a conventional chemistry panel – with a rapid molecular-panel assay allows healthcare professionals to begin treatment quickly and fine-tune later based on broader evidence.

What's next for sepsis testing

Ongoing innovation in the sepsis testing realm is cause for optimism. It should become possible in the very near future to significantly improve patient outcomes based on generating clinically actionable information in a much shorter timeframe. Any measurable reduction in mortality rates associated with sepsis would represent a major step forward in the delivery of healthcare.

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Sherry Dunbar, MBA, PhD, serves as Senior Director of Global Scientific Affairs for **Luminex.**

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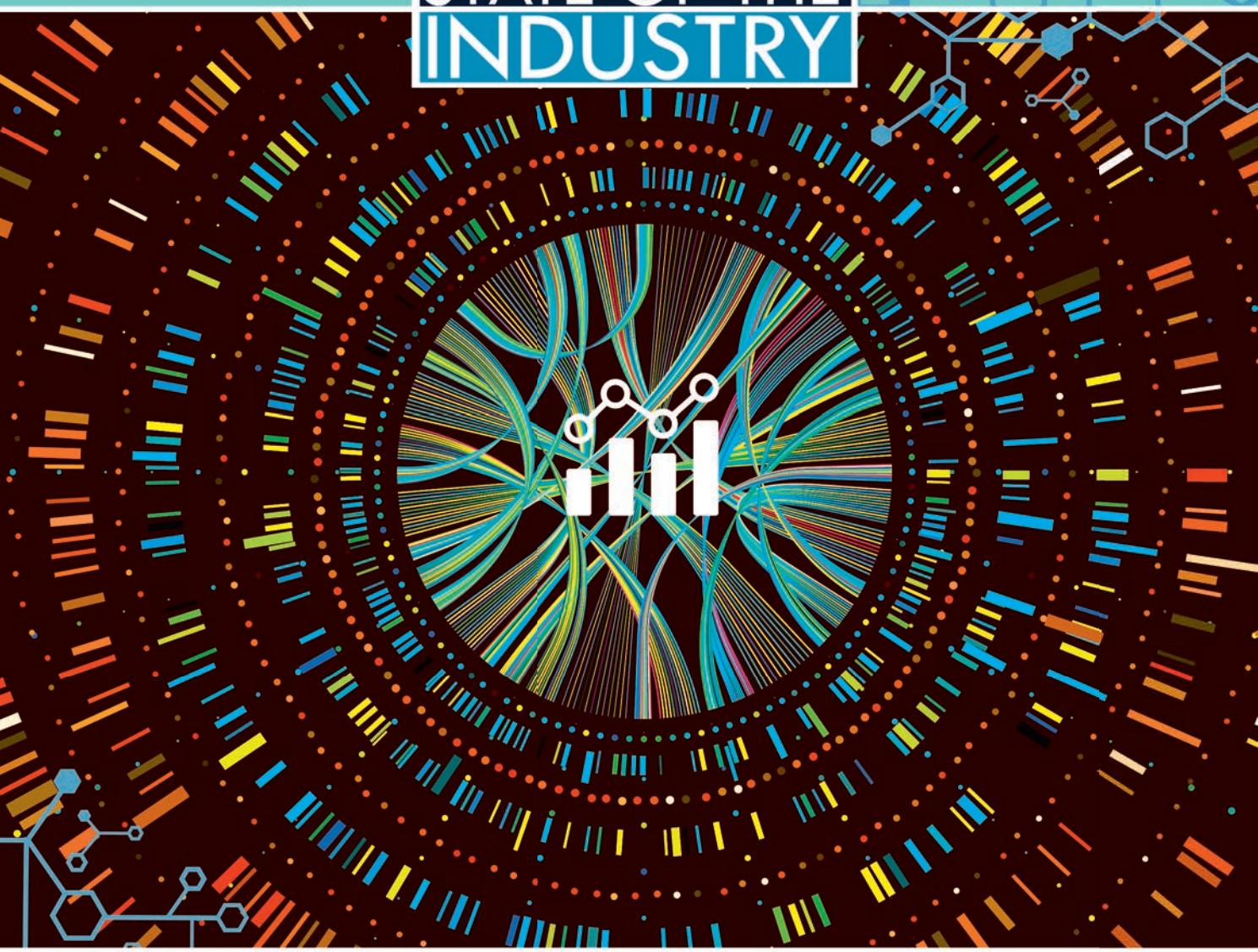

CLINICAL ANALYTICS

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Lab administrators prioritize accurate and timely financial and operational performance

by Kara Nadeau

While clinical labs have long faced operational challenges and financial pressures, the magnitude of these issues during the COVID-19 pandemic has been unprecedented. Clinical lab administrators face shrinking reimbursements, staff shortages and supply chain disruptions at a time when test volumes are through the roof. The ability to perform accurate and timely analytics on operational and financial performance has never been more critical.

In our first of four "State of the Industry" survey topics for 2021, MLO explored clinical data analytics adoption among labs, including opportunities to leverage analytics to support lab operation and management, and factors holding them back from data-based performance improvement initiatives.

Among survey respondents, 62% are in leadership positions, such as lab managers, administrators, supervisors, lab directors and section/department managers, with most working in hospital labs. The remaining respondents represent a broad range of job functions across a variety of facilities and lab sizes.

THE DEMAND FOR ADVANCED ANALYTICS

The role of clinical labs has evolved to meet the growing demands of healthcare. Their work goes far beyond the running of tests. Labs today must have the ability to support initiatives around value-based care and pay for performance. This means the capability to perform advanced analytics, says Tracy Roth, MBA, Senior Director, Product Management, Data and Analytics, Sunquest Information Systems:

> "Long gone are the days of producing test results in the hospital basement. Today's clinical laboratories are expected to lead evolving strategies in diagnostics, treatment and cost efficiency; these include optimizing operational effectiveness and test turnaround time, meeting value-based healthcare reimbursement targets, and exceeding consumer expectations. The practice of data analytics is at the core of these requirements and provides the roadmap for laboratory success."

As healthcare in general has been forced to rethink its approach to patient care, labs too must transform their strategies to support new care delivery models, according to Kim Futrell, MT(ASCP), MSHI, Senior Strategic Marketing Manager, Orchard Software Corporation:

> "Changes within the healthcare system are pressuring laboratory professionals to update their thinking and focus on a broader scope of laboratory stewardship. Laboratories are encouraged to find specific ways to contribute in a value-based, patient-centered healthcare system, which includes leveraging data analytics

– supporting population health initiatives and determining downstream impact of laboratory contributions."

With value-based care comes the demand for labs to generate information that can help healthcare organizations improve clinical effectives and care outcomes, explains Joseph Chiweshe, MD, MPH, Senior Manager at Beckman Coulter:

"We are in the midst of an expanding shift for our care models to improve the cost of healthcare and better align patient outcomes with impact for value. Organizations seek solutions that measure patient progress, provider performance and costs to advance health which are closely tied to lab operations, quality and management. Furthermore, COVID-19 has changed how labs must operate from having to implement contingency planning for at risk or infected staff in the face of existing labor shortages."

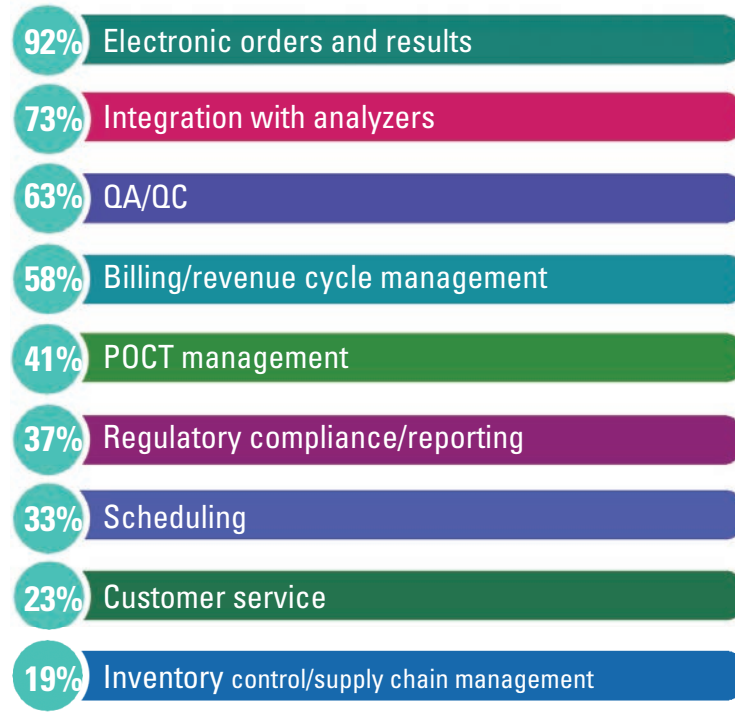
The use of data analytics can help labs operate more effectively and efficiently at a time when their services are needed more than ever, says Jamie Gramz, Head of Digitalization from Siemens Healthineers:

"There are several factors that are driving the use of data analytics to assess and improve lab operations. These include the overall need to do more with less in order to address staffing challenges, reduce costs, improve turnaround times, satisfy compliance requirements and accommodate the increasing demand for laboratory testing."

MOVING BEYOND MANUAL PROCESSES

In an effort to operate more efficiently and maximize existing staff resources, clinical labs have increasingly been transitioning from manual to electronic processes. As of January 1, 2021, Medicare is paying higher rates to labs that can turn around SARS-CoV-2 virus testing results within two calendar days of the specimen being collected;[1] therefore, labs have a strong financial incentive to secure results faster.

ELECTRONIC FUNCTIONS THROUGH LIS

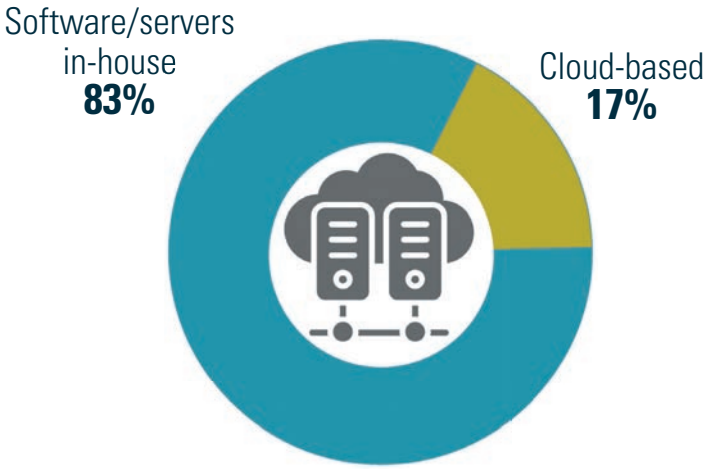


Nearly all survey respondents (92%) say their labs process orders and results electronically through their laboratory information systems (LIS). Also high on the list of LIS electronic functions are integration with analyzers (73%), quality assurance/quality control (63%), and billing/revenue cycle management (58%). Fewer respondents say their labs are electronically processing point-of-care testing (POCT) management (41%), regulatory compliance/reporting (37%), scheduling (33%), customer service (23%) and inventory control/supply chain management (19%) functions.

With regards to their LIS platforms, 61% of respondents say their labs use a module

within an enterprise-wide electronic health record system, while 39% use stand-alone systems. A growing number of labs are adopting cloud-based LIS systems (17%), with 83% still using in-house software/servers.

TYPE OF LIS INFRASTRUCTURE



As Gramz points out, a lab must be able to quickly and easily connect and integrate its LIS platform with many different analyzers and systems, which generate huge amounts of data. To support this integration, he recommends that labs employ systems with open connectivity and leverage middleware.

> "Open connectivity and the use of middleware play a key role in empowering labs to interface analyzers from the manufacturer of their choice for multidisciplinary testing," said Gramz. "By leveraging integrated data management, labs can also visualize testing status with alerting capabilities to help to create awareness and drive action."

Although labs are increasingly integrating internal systems and adopting cloud-based technologies, more than half (53%) say interoperability and data integration issues with LIS or electronic health records are still "stumbling blocks" to implementing electronic processes.

> "To overcome these challenges, the important first step is to clearly define the data and analytic needs of the laboratory, as well as those of stakeholders and how they align with the health systems goals and needs" said Roth. "Then, collaborate with trusted technology partners to bridge this gap. This partner must be well-versed in the complexities of laboratory workflow and data output."

Clinical lab leaders recognize the critical role of technology in supporting operations, and the need for improvements in this area. When asked to name their strategic priorities for their organizations in the next three years, the two top ranking responses were infrastructure and platform development (31%) and data analytics optimization to support lab management (25%).

Rick Callahan, VP Sales and Marketing, NovoPath, recommends purchasing laboratory equipment and software that conforms to HL7 (Health Level-7) standards to support standardization of data sharing between systems. He also recommends selecting hardware and software vendors that have previously worked together on interfacing their solutions in order to pave the way for system integration.

INTEROPERABILITY AND DATA INTEGRATION ISSUES IN IMPLEMENTING ELECTRONIC PROCESSES

To ensure current technology platforms enable the lab to meet customer demands Chiweshe recommends the lab, in conjunction with a trusted in vitro diagnostic (IVD) partner, constantly challenge the middleware, LIS and the EHR systems to develop efficient ways to:

- Help clinicians identify abnormal and clinically actionable results
- Reduce waste and operational redundancies
- Cater to quality metrics that reward performance
- Assist with change in volume demand
- Improve speed and accuracy of patient test results
- Maintain standardization across the system

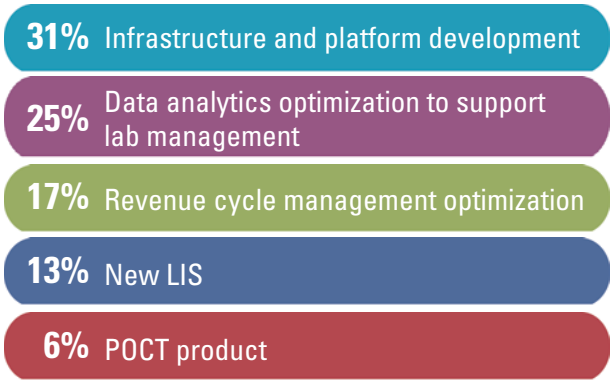
"Lastly, if you should employ a third party to develop interfaces with your software/hardware, hire an organization that is well established and experienced," said Callahan. "They are more likely to have interfaced to the same hardware/software that you are trying to interface with."

DATA-DRIVEN DECISIONS

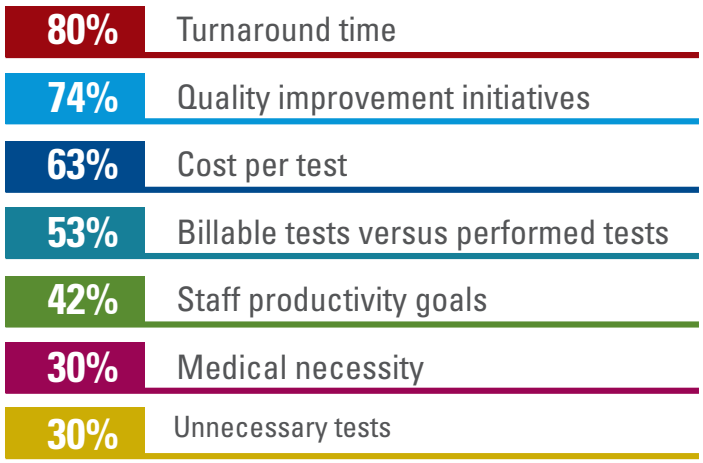
Those labs with access to accurate, timely and comprehensive data have the ability to perform advanced analytics for continuous improvement. According to Chiweshe, some of the benefits that clinical labs can gain from advanced analytics include:

- Increased efficiency and effectiveness of lab operations and patient care[2]
- Optimized costs
- Improved turnaround times
- Increased workflow efficiency

TOP IT PRIORITIES FOR THE NEXT THREE YEARS



OPERATIONAL PERFORMANCE INDICATORS



- More efficient use of staff time
- Better collaboration with healthcare partners outside the laboratory

The establishment and measurement of key performance indicators (KPIs) helps to identify and address shortcomings, gaps and waste. The most commonly used operational performance indicators among those surveyed included turnaround time and quality improvement initiatives. One-third of respondents also measure the number of medically necessary tests and unnecessary tests.

"Analytics play a crucial role in empowering laboratories to assess performance, identify inefficiencies and determine the root cause of problems," said Gramz. "It enables the lab to quickly and easily benchmark performance and drive continuous improvement with the ability to monitor common KPIs through use of reports for turnaround time (TAT), TAT exceptions, throughput, reagent efficiency, automation utilization, auto-validation rates, hemolysis, problem samples and other key metrics important to the laboratory."

The survey revealed that most clinical labs use analytics to support lab operations. More than half (66%) of those surveyed said they

Photo from AdobeStock

use data analytics for at least some aspects of lab management, with 11% using analytics for all aspects, and 53% using it for some and planning more. The majority of labs use data analytics tools that are integrated with their LIS (65%), while 35% use a separate tool.

The reliability and usefulness of analytics are only as good as the data backing them. The fresher the data, the more relevant the results. Among those using data analytics in their operations, nearly one-third (29%) say they use real-time data, 10% say their data is refreshed by hours/minutes, 28% daily and 33% weekly.

"We are looking at a future where IT systems can analyze databases with genome analyses from hundreds of patients for trends that aid in determining the best treatment plans," said Futrell. "This future role of the laboratorian is expected to shift away from specimen handling toward data processing and interpretive guidance."

COVID-19

When asked what metrics their labs are tracking specific to COVID-19, the top areas were positive and negative test results (37%) and number of tests performed (33%), followed by turnaround time (14%), suppliers used/inventory management (7%), type of test performed (6%) and cost per test (4%).

The COVID-19 pandemic has elevated the importance of analytics, according to Carl Smith, General Manager, Lab Division, CompuGroup Medical U.S.

> "Due to the COVID-19 pandemic, analytics have become more important than ever," said Smith. "Labs are the healthcare industry's key resource for proper diagnosis and treatment. As vendors, we need to ensure that all data is accessible. We must provide the data analytics needed to assist with the current situation and establish the systems that will empower laboratories to manage all future pandemics."

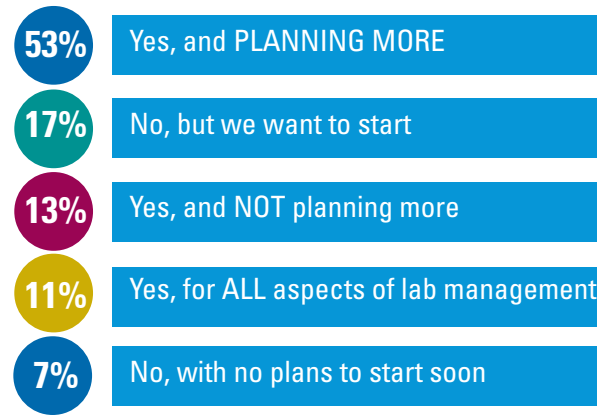
One area that has been hit hard by the pandemic is staffing, explains Callahan, prompting many labs to "rethink" how they operate. He states:

> "Some facilities are working with reduced staff due to hiring freezes imposed by management, employees working from home, attrition and quarantined personnel. These labs need to analyze the way they do business, and with the results of the analysis, 'rethink' the way they have done business in the past, so that they can ensure patient safety, accurate results, timely turnaround time, as well as their external client's satisfaction."

PLANNING AND FORECASTING

Visibility into existing processes, supplies and staffing are necessary for labs to identify shortcomings, gaps and waste, and plan accordingly for the future to boost operational and financial performance. When it comes to management forecasting, test utilization was highest on the list (67%) of tests that labs perform, followed by workloads (60%), staffing levels (54%) and supply utilization (43%).

USE OF DATA ANALYTICS TO SUPPORT LAB OPERATION & MANAGEMENT



The majority (68%) of labs use an electronic tool for management forecasting. About half (54%) incorporate data from other departments (e.g., finance, ED, inpatient units) into measurement for performance improvement initiatives or planning for capital expenditures.

With regards to challenges currently faced, or those they will face in the next three years with regards to planning and forecasting, the top ranking responses were staffing (56%), funding (44%), ROI/costs (20%), training (15%) and technology (9%).

As Roth points out, advancements in analytics and the ability to better plan and forecast offers ways for a clinical lab to differentiate itself from the competition.

> "Laboratory results are a critical component of patient diagnostics, treatment decisions and disease surveillance," said Roth. "Accessible data and timely metrics offer laboratories a differentiator – the opportunity to identify drivers of efficiency, optimize their revenue models, plan for future changes in volume, and create their value story within the healthcare ecosystem. Additionally, transformative laboratory analytics can anticipate changes in patient

acuity and population health risk, which ultimately leads to improved physician decision-making, patient health outcomes and cost efficiency."

THE ROAD AHEAD

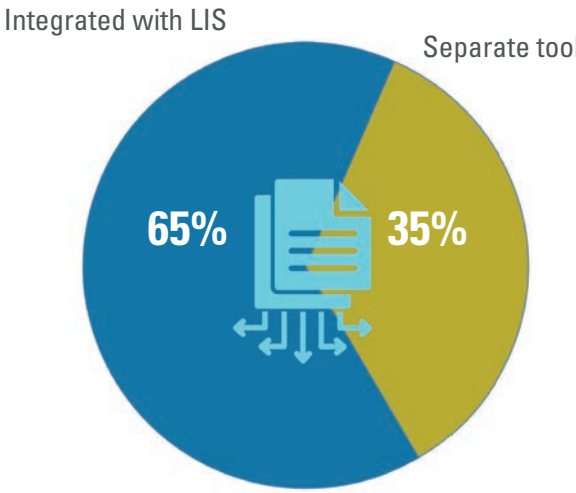
The healthcare industry has long struggled to adapt to value-based care and payment models, with a growing reliance on clinical labs to provide analytics to support data-driven decisions. The emergence of COVID-19 has only added fuel to the fire as labs, already facing staffing shortages and pressures to operate more efficiently, have been pushed to their limits.

In order for clinical labs to meet current and future demands in patient care, Futrell says they must break down existing barriers and proceed with a more holistic approach, stating:

"Laboratory professionals and healthcare workers in general must stop thinking and functioning in silos and think in terms of patient-centered care. Secondly, laboratories need an informatics partner that can integrate everything lab-related across their organization. Partner with your IT staff to gain an understanding of how the lab system fits within the overall organizational architecture."

Futrell also believes that optimal use of laboratory data can help laboratory professionals gain greater visibility, recognition and respect that has long been denied.

TYPES OF DATA ANALYTICS TOOLS



"A more comprehensive understanding of how laboratory data contributes to patient care can boost the laboratory's value-add and contribution," she said. "With IT, molecular and genetic testing advances, the lab is slowly transitioning away from hands-on processes to a reality where the specimen is rarely touched. What the laboratorian will 'touch' is the data – being involved in valuable interpretations, test consultations and algorithms, and lab informatics."

In looking towards the future, Smith references how clinical labs are embracing the Clinical Lab 2.0 movement, with its focus on data analytics as a way to support value-based care. In describing this movement, the Clinical Lab Management Association (CLMA) explains how leading health systems are leveraging "the massive real-time data emanating from their in-system laboratory services to drive better patient outcomes on a more cost-effective basis, close gaps-in-care, and improve revenue cycle and value-based payments at the system level."[3]

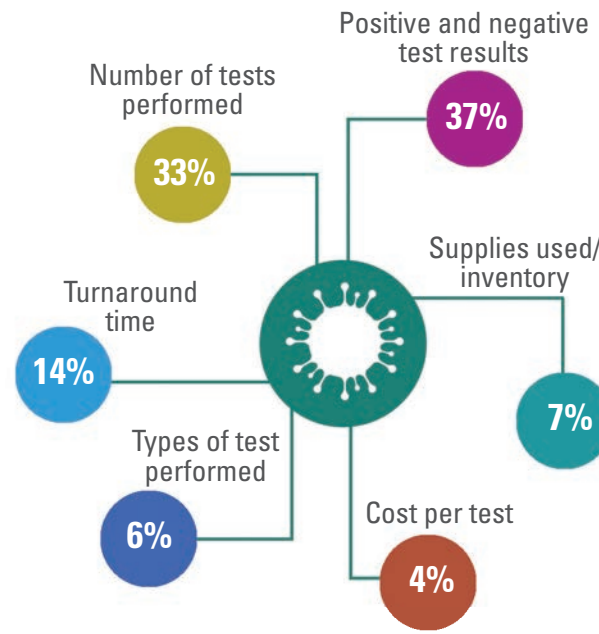
"We work with industry experts and clients to build a platform for the Lab 2.0 concept, which emphasizes using laboratory data to produce actionable insight that can lead to better patient outcomes," says Smith. "For example, CGM develops customized reporting for its lab clients. Armed with these reports, labs can provide physicians with the analytics to assist with predictive modeling, improving the long-term care that patients receive."

For clinical laboratories wanting to improve their operational workflow and achieve optimal lab administration, Callahan recommends taking a Lean Six Sigma approach.

"While I would recommend that you conduct a thorough Six Sigma Analysis for the entire laboratory operation, this process is very time consuming," said Callahan. "You can instead break down the lab into functional 'areas' and select areas one at a time to focus in on and work the Six Sigma process."

"Start by defining the workflow in the area, develop a measurement for the tasks in the defined area (volume, time to

METRICS TRACKED FOR COVID-19



complete, error rate etc.), analyze what was defined and measured and look for ways to improve the metrics in that area," Callahan explains. "Then, move onto the next functional group making sure that those previously defined continue to improve in their processes. With this, your lab will become more efficient, you will reduce your costs, reduce the probability of laboratory error, increase staff and client satisfaction all at the same time you'll be learning how to do more with less."

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Best practices in capillary blood collection

By Nancy Glasgow-Roberts, PBT (ASCP)

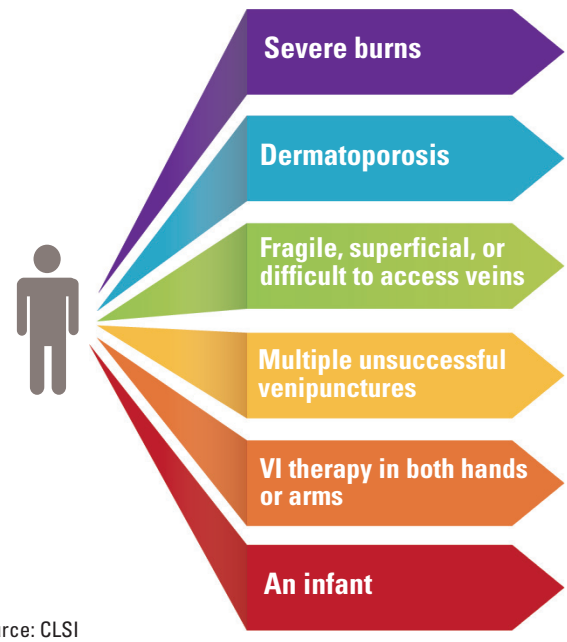
Capillary blood sampling is an essential method of blood collection performed by medical professionals of all skill levels and disciplines with diverse titles such as phlebotomist, patient care technician, medical assistant, nurse, lab assistant, lab tech, med tech and many others. Accuracy of results greatly depends on education and standardization of the sample collection technique.

Capillary blood collection is just as much a part of patient care as a tonsil or gallbladder surgery or any other invasive or non-invasive procedure. The specimen is a part of the patient and should be treated as such. Collecting capillary blood specimens requires patience, education, and a good technique. When facilities provide continuing education, standard updates, and quality equipment, lab employees can work toward collecting high-quality specimens. Any new or modified policies or processes within a laboratory's own workflow may require education and training for the staff.

Proper capillary blood collection and handling procedures are critical to accurately reflect a patient's physiology. In September 2020, the Clinical and Laboratory Standards Institute (CLSI) published the updated capillary standards (GP42-Collection of Capillary Blood Specimens).[1] This was the first revision in 12 years.[2] The standards provide guidance for proper capillary blood collection procedures and processes to ensure the safety of the patient as well as the healthcare professional responsible for collecting blood specimens. Maintaining a standard collection procedure is important because it will help reduce pre-examination errors.

This article describes some of the best practices for capillary blood collection and handling included in the updated standards.

Capillary puncture collection may be a good choice if patients have one of the following characteristics:



Source: CLSI

Reasons for capillary blood collection

Capillary punctures are better suited than venipuncture in certain situations. For example, performing a venipuncture on infants can be difficult and potentially hazardous because these patients have smaller veins and tend to move more than older patients during the procedure. With a capillary puncture, a small but adequate amount of blood for laboratory examinations can be obtained. Although a capillary puncture can limit iatrogenic anemia, it does not eliminate the need to monitor blood volume removed from pediatric patients. Age and weight should be considered when the appropriate site for capillary puncture is selected in pediatric patients. Capillary blood specimens should be collected into appropriate capillary collection devices and not collected and or transferred into venipuncture tubes.

Adult patients may require a capillary puncture collection due to fragile, superficial, or difficult to access veins, if they have undergone multiple unsuccessful venipunctures, or if the requested test requires a small volume of blood. Other patients that may require capillary blood collection include burn patients or patients with dermatoporosis, which refers to issues common to aging skin. Patients with veins that are being preserved for IV therapy or if they are receiving IV therapy in both arms or hands also could benefit from capillary puncture collection. In these situations, the sites that should be used are the palmar surface of the distal segment of the middle or ring finger.

Site selection

There are sites that must not be used, such as infected sites, because of the potential for altered examination results, aggravation of infection as well as patient discomfort. There also are sites that require a physician's permission, such as limbs on the side of a mastectomy, due to the risk of lymphedema and potential for altered examination results. Sites that should be avoided include areas with extensive scarring, healed burns, inflamed sites, edematous sites, previous puncture sites, earlobes and thumbs.

Such terms as "needs to," "must," "require" and "should" are used to explain how medical professionals should perform capillary blood collection procedures. Some of these actions are not a choice. For example, punctures must not be performed on the posterior curvature of the heel or toes other than the great toe or the area of the arch.

A heelstick capillary blood collection also requires the collector to consider the clinical condition of the patient as well as age and weight when choosing this site and when

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choosing a lancet that offers the depth of the puncture. Punctures 2.0 mm deep or less will provide adequate blood flow without risking bone injury.

Following a guideline with proper locations offers the least risk of puncturing the heel bone. If such areas as the lateral and medial surfaces of the heel have been repeatedly punctured or if bruising is extensive in these areas, a venipuncture may need to be considered.

Capillary blood collection from fingers is acceptable for adults and older children. However, fingers of newborns and infants less than 6 months of age must not be used for capillary blood collection because the distance from the capillary surface to the bone in the thickest portion of the last segment of each finger in newborns varies from only 1.2 to 2.2 mm. In newborns, local infection and gangrene are also potential complications of finger punctures. For pediatric patients between 6 and 12 months of age, the decision to use the finger instead of the heel must be based on weight. In infants weighing more than 10kg (~22 pounds), the finger can be used if the lancet depth does not exceed 1.5 mm.

Lancet Selection

Care must be taken not to shorten the distance between the skin and bone by compressing the tissue before the spring-loaded lancet activation. This may be difficult to do depending on the lancet your facility has chosen to use.

The manufacturer's instructions must be followed for orientation of the lancet. The puncture should be made across the prints, which allows large drops of blood to form. If the incision is made going with the print instead of across, the blood will run down the grooves of the print and this becomes messy and wastes blood that could be collected if done properly.

Site preparation

Warming the site increases arterial blood flow to the site up to sevenfold and will not burn the skin if warmed at a temperature no higher than 42 degrees Celsius. Although studies show that pre-warming might not be necessary when an incision device is being used, increasing capillary blood flow through pre-warming can minimize the necessity to exert additional pressure to the site.

Cleansing the site is performed to minimize microbiological contamination of the specimen and patient infection. Allowing the site to dry, without wiping it dry, enables optimal decontamination while reducing the potential to interfere with the specimen and prevents the patient from experiencing a burning sensation when the puncture or incision is performed.

Policies and procedures

Some medical professionals have been performing capillary collection procedures for their entire career. Even so, there are a few things that demand attention when updating a facility's own policies and procedures. For example, information on positioning the patient received only one line on one page in the previous document, but the new standard awards this topic quite a bit of well-deserved real estate.

In the past, some of our blood collection procedures resulted in clots within the anticoagulant tubes. That is why an important addition to any laboratory's guidelines or standard operating procedures (SOP) is a suggestion to carefully mix the specimen periodically during collection to avoid clotting.

Intermittent gentle pressure may be necessary to obtain an adequate specimen. Pressure should be released between drops to enable the capillary beds to refill and then be reapplied and repeated until the required specimen volume is reached.

Order of the draw

There are important reasons to follow the order of draw during capillary blood collection. For example, beginning with the EDTA capillary blood tube ensures that the blood will not begin to clot before the specimen is collected. Clots in this tube will certainly affect the accuracy of the blood count. For both glass and plastic microcollection tubes during a single capillary puncture, the order of the blood draw is as follows:

- Capillary blood gas (CBG)
- EDTA tube
- Other additive tubes
- Nonadditive tubes
- Filter paper for DBS collections

Collection tubes

Having a greater understanding on how to properly collect blood into a capillary tube – also referred to as a straw – is important for collecting a CBG or when using a microcollection tube that is devised with a straw for the collection. Holding the capillary tube at a slight angle upwards to prevent any air bubbles from entering the tube is an accurate and important detail to include in a standardized technique.

Post collection care

It is important to apply pressure to the site after collection is complete by slightly elevating the extremity until bleeding has stopped. Continue to observe the site and the patient to be certain no adverse effects need to be reported. Label the specimen immediately after collection and in the presence of the patient and by the same person who collected the specimen. Of course, gloves and any other required personal protective equipment must be worn during collection, labeling, and preparation for transport.

In conclusion, establishing a step-by-step, updated, standard procedure within a facility is essential to help eliminate collection errors as well as improve the quality of care for the patient.

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Nancy Glasgow-Roberts, PBT (ASCP), chaired **CLSI**'s most recent document development committee for the Collection of Capillary Blood Specimens, 7th edition. She also helps facilities update their policies and procedures for blood collection.

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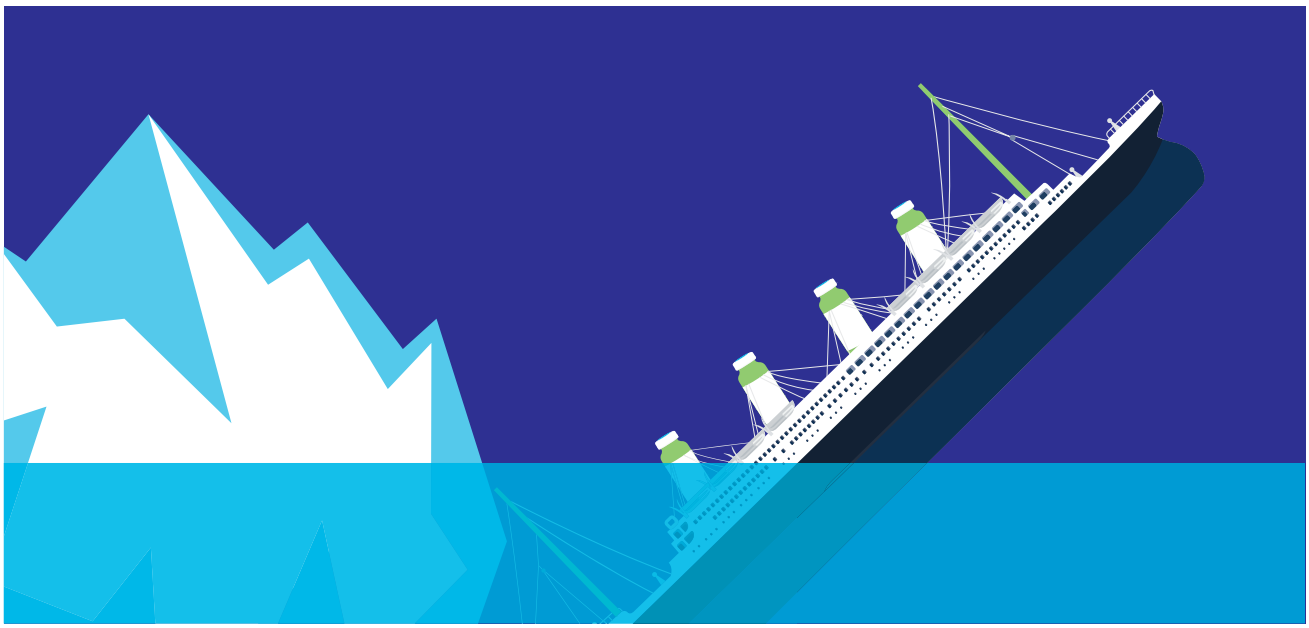

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Patient safety monitoring in international laboratories

By Department of Pathology at the Johns Hopkins University School of Medicine

International travel, teaching and improving laboratory quality worldwide may not describe the responsibilities of most laboratory professionals, however, medical technologists working for the Johns Hopkins University (JHU) Patient Safety Monitoring in International Laboratories (pSMILE) program have taken their clinical laboratory training and skills beyond the bench.

JHU-pSMILE is a National Institutes of Health (NIH) resource designed to evaluate and develop the capability of laboratories to participate in prevention, vaccination and therapeutic clinical studies conducted in developing countries and supported by the National Institute of Allergy and Infectious Diseases (NIAID). Designed to provide long term support to developing countries with the design and implementation of HIV/AIDS prevention and treatment research studies relevant to their populations, the program ensures the integrity and reliability of laboratory tests for monitoring the safety and efficacy of experimental products investigated in studies funded by the Division of AIDS (DAIDS) at NIAID. The pSMILE program has been operating at the Johns Hopkins University School of Medicine, Department of Pathology since the inaugural contract was awarded in 2004.

The four core functions of pSMILE are:

- Monitoring laboratories' compliance with Good Clinical Laboratory Practice Standards (GCLP)
- Monitoring the ability of laboratories to reliably perform protocol-specified laboratory testing
- Providing laboratories with various means of assistance, guidance and training to address and prevent recurrence of deficiencies in GCLP and/or Proficiency Testing (PT) to improve quality of laboratory operations
- Hosting and maintaining a computerized data-management system and document library that includes laboratory performance data and guidance and resource documents

The JHU-pSMILE team has developed processes, standard operating procedures (SOPs) and software systems to accomplish these four core functions. Over the past sixteen years, the program has grown into an organization that is internationally recognized for its quality assurance methods. In July of 2020, JHU-pSMILE was awarded International Organization for Standardization (ISO) 9001:2015 certification. The ISO 9001:2015 standard ensures that products and services meet the needs of clients through an effective quality management system. As part of the ISO 9001:2015 certification process, JHU-pSMILE developed and implemented a quality management system to improve overall performance and maintain a high-level of quality and strong customer service.

Throughout the 16-year history of the program, the team has supported 285 laboratories in 31 different countries (**Figure 1**), providing expert laboratory assistance for patient-safety testing. Currently, pSMILE actively supports 144 international laboratories in 18 countries including: 30 in South America, 38 in East Africa, 41 in South Africa, seven in Southern Africa, two in the Caribbean, 25 in Asia and one in Europe.

Laboratories are selected for pSMILE support because they are performing NIAID-sponsored research for HIV/AIDS and its related co-infections and co-morbidities. Research protocols are administered through HIV Clinical Trials Networks such as the AIDS Clinical Trials Group (ACTG), International Maternal Pediatric Adolescent AIDS Clinical Trials Network (IMPAACT), HIV Prevention Trials Network (HPTN), HIV Vaccine Trials Network (HVTN), and Microbicide Trials Network (MTN).

Throughout the tenure of the program, pSMILE has been able to support the laboratories and the study participants in the network protocols of hundreds of different clinical trials. Each network focuses on a specific aspect of HIV research, as the names of the networks indicate:

- HPTN is dedicated to the prevention of HIV and has been responsible for advancing prevention protocols, such as the HPTN 052 study, which proved that early antiretroviral therapy (ART) can prevent HIV transmission. ART was named a 2011 Breakthrough of the Year by the journal *Science*.

Continent	Country	# Labs
Africa	Botswana	5
	eSwatini	1
	Ethiopia	2
	Kenya	11
	Malawi	7
	Mozambique	1
	Senegal	2
	South Africa	66
	Tanzania	6
	Uganda	15
	Zambia	1
	Zimbabwe	5
Asia	Cambodia	9
	China	4
	India	14
	Philippines	2
	Thailand	24
	Vietnam	2
Europe	Switzerland	1
North America	Costa Rica	3
	Dominican Republic	1
	Haiti	2
	Jamaica	2
	Mexico	1
	Panama	3
	Puerto Rico	1
	United States	16
South America	Argentina	8
	Brazil	39
	Colombia	2
	Ecuador	3
	Peru	14

Figure 1- pSMILE's global footprint showing countries with current and previous pSMILE activity.

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- The IMPAACT network has been credited with developing protocols that greatly reduce the transmission of HIV from mother to baby through its many maternal and infant studies.
- The MTN network's agenda focuses on microbicides and was responsible for the CAPRISA 004 study, which was the first study to show that the use of microbicides as pre-exposure prophylaxis (PrEP) could be effective.
- The ACTG network's agenda primarily revolves around the treatment of HIV and its co-infections, especially TB. The ACTG network is credited with developing protocols proving that combinations of anti-HIV medications control HIV better than single drug regimens.
- The HVTN network is dedicated to the search for a vaccine against HIV and has recently launched protocols that include mosaic vaccines, which is a new concept for HIV vaccines. The experimental vaccine contains a medley or mosaic of genes from various HIV subtypes. The HVTN is also working in collaboration with the HPTN on the novel concept of using Antibody Mediated Prevention (AMP) to prevent HIV infection.

pSMILE also supports non-network studies funded by DAIDS. For example, pSMILE helped laboratories that participated in the iPrEx studies, led by Robert Grant, MD, MPH at the University of California – San Francisco, who was named by *Time* magazine as one of 2012's most influential people. Grant led the groundbreaking, global study that showed how existing HIV/AIDS medications could effectively be used to prevent transmission of HIV in those likely to be exposed to the virus. pSMILE also supported the laboratories participating in the Comprehensive International Program of Research on AIDS (CIPRA). The goals of the CIPRA study focused primarily on capacity building by supporting the training and infrastructure necessary for developing and sustaining ongoing research efforts.

In recent years, JHU-pSMILE has also been called upon to assist with emerging infectious diseases, such as the Zika virus outbreak in 2016 and the SARS CoV-2 pandemic in 2020.

pSMILE overview

The pSMILE resource is managed by the NIH Division of AIDS by a contracting officer's representative (COR) who administers and directs all activities. At JHU, pSMILE activities are led by a principal investigator and a project manager who oversee daily operations and staff including:

- Ten registered medical laboratory scientists who serve as international QA/QC coordinators
- A program officer managing financial accounting and invoicing
- A programmer analyst providing website development and management
- An administrative coordinator performing administrative and clerical functions
- Information technology consultants providing targeted specialties and expertise as needed

This dedicated team of professionals comes from diverse cultural backgrounds and speak multiple languages, providing a unique basis of understanding and pertinent global sensitivity, which is beneficial to pSMILE's international mission. Members of the current JHU-pSMILE team have worked in the field of pathology and laboratory medicine, ranging from 12 to 40 years in both the United States and globally, and have a combined total of greater than 200 years of laboratory experience. JHU-pSMILE coordinators are credentialed by a range of clinical laboratory certifying bodies, including the American Society for Clinical Pathology (ASCP) and American Medical Technologists (AMT). JHU-pSMILE also has a team member who holds certification from the American Society for Quality (ASQ) as a certified quality process analyst (CQPA). The team members' laboratory experience is as varied as their educational and cultural backgrounds, ranging from large university hospital laboratories, commercial laboratories, international research and clinical laboratories, doctor's office laboratories and more. They also have a wide range of knowledge and practical experience covering nearly every specialty in the clinical laboratory, including chemistry, hematology, immunology, flow cytometry, serology, microbiology, mycobacteriology, histology/cytology, and blood banking. Team members also possess advanced degrees, such as in business, distance education and biotechnology.

JHU-pSMILE coordinator training and responsibilities

To develop the skills required to be a JHU-pSMILE coordinator, new employees complete a rigorous training program. They receive training on all pSMILE internal procedures and are mentored by assigned trainers who are experienced members of the JHU-pSMILE team. By using a virtual education platform, training is standardized, comprehensive, and inclusive of all pSMILE tasks including proficiency testing review, laboratory audit review and creation of remediation action plans, instrument validation, and international laboratory visits. Since this job is unlike many in the clinical laboratory profession, it typically takes about a year to complete the training of a new pSMILE coordinator.

The day-to-day work of a JHU-pSMILE coordinator typically involves a few key tasks that almost always provide an exciting challenge. pSMILE's approximately 144 global laboratories are divided among coordinators for everyday activities, including evaluating, analyzing and reviewing proficiency testing data, assisting with audit remediation, reviewing instrument validation and assisting with other laboratory quality issues. Coordinators also work with laboratory sites to track PT shipments as well as resolve shipping and results submission problems.

Laboratory proficiency testing

Each international laboratory is required to complete the same level of proficiency testing as is required for U.S. laboratories. pSMILE provides PT surveys, evaluates results, and follows up with a written review. Coordinators also work with laboratories on resolving PT failures with resolutions documented as part of an investigation report (IR).

pSMILE acts as a facilitator, purchasing and evaluating PT for hundreds of laboratories with a primary research focus on HIV diagnostics. As such, pSMILE is in a unique position to identify challenges and stay abreast of emerging technologies as they relate to HIV diagnostic assays and proficiency testing. In 2004 when pSMILE began monitoring HIV testing for NIH, the state-of-the-art assays were 2nd and 3rd generation enzyme-linked immunosorbent assay (ELISA) methods, with western blot being the gold standard confirmatory assay. pSMILE worked with PT providers, such as the College of American Pathologists (CAP), to ensure that peer groups and evaluation methods were sufficient for these methods. pSMILE also developed evaluation criteria for western blot bands, which were not evaluated by the PT provider, because this information was critical to HVTN protocols. As 4th generation and p24 antigen methods emerged in more and more research protocols, pSMILE again worked with PT providers, including international providers, to ensure adequate coverage and evaluation. We have now seen almost complete discontinuation of the use of western blot in research protocols, with the emergence of rapid confirmatory assays. This has provided new challenges in proficiency testing, which pSMILE has been able to overcome by using a combination of PT providers and by giving feedback to the providers to help them improve their coverage.

Many pSMILE laboratory sites participate in CAP's PT programs.

However, over the years, PT programs from other countries have also been utilized since they may provide better peer groups for international laboratories or may be better suited to assays being performed in international settings. A good example is tuberculosis (TB) testing. Since TB is more prevalent internationally than in the United States, comprehensive and robust PT material is not readily available domestically. JHU sources PT panels from Germany and France to ensure adequate PT coverage for TB culture, identification and drug susceptibility testing (DST). In addition, there are TB diagnostic methods that are widely used outside of the United States, so pSMILE utilizes PT panels from a South African source because it has developed panels that are specifically customized and validated for these methods. In the case of Interferon Gamma Release Assays (IGRA), JHU-pSMILE discovered that the U.S.-based PT was inadequate to cover the assay as it is utilized in network studies. More rigorous coverage was found utilizing panels produced in Sheffield, United Kingdom.

pSMILE also provides PT when products are not available commercially or are insufficient. For example, in response to a lack of commercially available PT, JHU-pSMILE developed vaginal wet mount microscopy PT utilizing digital images available through an online training program. This PT program assures the ability of laboratories to identify Trichomonas Vaginalis and vaginal clue cells, a critical component of one of the research protocols supported by pSMILE.

A laboratory audit performed by an independent DAIDS contractor is an entry point for new laboratories. Audits are generally performed annually for established laboratories and are based on DAIDS GCLP guidelines, which are very similar to CAP accreditation checklists. Audit reports are then sent to pSMILE for review and preparation of an action plan that guides the laboratory through the process of correcting each documented deficiency. This can sometimes be a lengthy process, involving many emails and web-based meetings between the pSMILE Coordinator and the site. The resolution of the action plan also provides opportunities for sites to improve their processes as well as for pSMILE coordinators to engage in formal and informal teaching and training.

Coordinator day-to-day work is interspersed with other responsibilities and challenges. Each coordinator generally participates in several internal and external committees working on a wide range of topics and projects. Internal committee charges include developing resources, designing pSMILE.org's website content, developing and testing software, developing protocols for instrument validation, and preparing conference and other educational materials. pSMILE also has an internal quality assurance committee that focuses on regulatory compliance, accreditation (such as ISO 9001), and the monitoring of pSMILE internal processes to ensure quality. External committees include the JHU Pathology Department's committees, such as the Diversity Committee or Annual Educational Symposium Committee. Team members also serve on research protocol working groups and participate in cross-network projects.

Tools of the Trade

JHU-pSMILE coordinators utilize a unique array of competencies. Extensive clinical laboratory experience is complemented with computer skills using software programs such as Microsoft Excel, Word, Teams, PowerPoint and SharePoint. Coordinators also use method validation tools and a web-based SOP management tool. In addition, JHU hosts and maintains multiple software systems that aid in managing all aspects of pSMILE functions and workflow. These web-based applications were developed in-house and include electronic document repositories, automated filing systems, and online data warehouses customized for optimal functionality and utility.

There are three primary software tools:

- Oversight Masterlist (OSML), a SQL database designed to organize and track laboratory-specific information. This is an internal application accessible only by pSMILE staff members. Examples of the comprehensive information stored for each laboratory include the location, contact information for leadership personnel, network affiliation and DAIDS oversight staff, and laboratory accreditation status.
- pSMILE.org website, a document repository that not only stores and posts laboratory-specific documents but also contains an extensive library of guidance and open-access resource documents. Resources include templates for SOPs and forms, checklists, Excel spreadsheets for calculations used in method validation studies, published articles, and web links.
- AutoSMILE, a tool built at JHU, is a database and web-based user interface for automating the review of laboratory proficiency testing data. This system provides proficiency testing reviews, summaries, and schedules that meet regulatory requirements governing clinical trials such as from the European Medicines Agency (EMA) and U.S. Food and Drug Administration (FDA). JHU has arranged for secure electronic transfer of proficiency testing data from each proficiency testing provider. JHU-pSMILE coordinators verify the providers' evaluation of the data and supply evaluations for ungraded results. The system derives a score based on the overall evaluation and determines whether the laboratory needs to complete a report for unacceptable results. The system then generates an investigative review report that the coordinator can edit as needed and send via email to all stakeholders, including the laboratories, network personnel, and representatives from DAIDS. A valuable feature of AutoSMILE is the ability to track and assess laboratory PT performance over several years. The database generates an Excel spreadsheet for each laboratory, summarizing the performance of each protocol analyte over the previous three years.

The AutoSMILE software has been extensively validated to ensure that data integrity is maintained and the system complies with standards. AutoSMILE not only allows for the efficient use of coordinators' time; the automated process also improves accuracy of transcription, standardizes the review of PT data, and provides timely and uniform reports to stakeholders.

International travel and teaching

Interfacing with the international laboratories on a daily basis is the key to the success of the pSMILE mission. Strong communication skills are important and cultural sensitivity goes a long way in establishing a connection and fostering collaboration. E-mail, telephone, and web-based conferencing are standard daily channels of communication. However, coordinators travel to selected laboratories throughout the year, averaging stays of one to three weeks. Laboratories are located primarily in developing, resource-constrained countries and personal safety while traveling is a priority. That is why coordinators typically travel in pairs. They spend most days in the laboratories, working side by side with our international counterparts to resolve problems, offer possible solutions, and share knowledge to help improve quality in the laboratory.

Each laboratory visit focuses on specific objectives. These may include instrument validation, assessment of laboratory testing capacity and methods, TB laboratory assessments, laboratory audit remediation, instrument/method troubleshooting, and other special assignments from the NIH sponsor. Training sessions for larger groups are often held while on-site, providing continuing education opportunities for both bench technologists and management staff. We also help and mentor laboratories to become accredited by agencies, such as CAP, South African National Accreditation System (SANAS), and ISO 15189. The work we accomplish during

these trips is rewarding, and we are proud that laboratories that we have supported are recognized as having high standards of quality by the NIH, clinical trials networks, and other regional laboratories.

Team members also participate in regional and international meetings and conferences that provide an opportunity to collaborate with researchers in the field of HIV/AIDS. Each of the clinical trials networks described earlier in this article conduct annual or biannual meetings to share their research and provide training to personnel involved in their trials. The pSMILE team regularly participates in these network meetings. JHU-pSMILE team members have provided educational seminars and presentations on a wide variety of topics related to laboratory quality assurance. Presentations have included such topics as method validation, evaluation of QC ranges, technical assistance for novel TB methods, and HIV proficiency testing. The JHU-pSMILE team has also given many presentations on laboratory safety, audit preparation, and developing Quality Management Systems. The JHU-pSMILE team also has been able to participate in and contribute to research studies and publications.[1-3]

Summary

The pSMILE program at JHU is a collaborative effort that ensures the quality of testing at international laboratories conducting clinical trials and studies. Although pSMILE was established to assist laboratories performing HIV/AIDS research, we are flexible enough to assist with emerging infectious diseases such as Zika and SARS CoV-2. pSMILE has provided an opportunity for interesting, fulfilling, and challenging alternative career paths in a non-laboratory, clinical research setting. We have been privileged to have a front row seat and play a role in breakthroughs in the prevention and treatment of HIV that changed the course of the history of the disease. The pSMILE resource, connecting the NIH Division of AIDS and the Johns Hopkins University, has enabled us to use our experience, skills, and education as laboratorians to go beyond the bench.

ACKNOWLEDGEMENTS

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ALCOR Scientific

Immunoassay instrument

The LUMIPULSE G1200 is a mid-sized fully automated immunoassay instrument, based on chemiluminescent enzyme immunoassay (CLEIA) technology. The analyzer processes 120 tests per hour and provides results in 30 minutes for all assays. It also allows for continuous loading and unloading of samples, reagents and consumables without operational interruption.

Fujirebio

HbA1c analyzer

The ADAMS A1c HA-8180V is a fully automated hemoglobin A1c analyzer that utilizes gold standard HPLC technology. The analyzer has the lowest CVs on market (≤1 percent), eliminates interference from the most common hemoglobin variants, features on-board sample mixing and eliminates routine chromatogram review.

ARKRAY

Molecular diagnostics system

The Panther molecular diagnostics system is a fully automated, sample-to-result platform that can be used in low-, medium- or high-throughput laboratories. With a small footprint, adaptable workflow options and consolidated testing menu, it combines women's health, sexually transmitted infections, viral load and respiratory virus testing, which can all be done simultaneously.

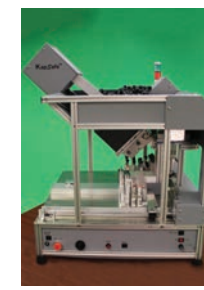
Hologic

Automation system

The DxA 5000 is a total laboratory automation system featuring a comprehensive pre-analytical specimen check system designed to identify up to 70 percent of the most common pre-analytical errors. The single point of entry supports various tube types and sizes for batch loading, with STAT samples having the highest priority.

Beckman Coulter

Recapping device



The bench-top KapSafe Recapper automates the process of recapping sample tubes of various heights at a throughput of 750 tubes/hour. KapSafe helps lab staff members eliminate their exposure to repetitive stress injury during manual recapping. It uses multi-tier caps to fit various tube diameters.

LGP Consulting

Film array system

The BioFire FilmArray Torch System is compatible with all existing infectious disease panels on the BioFire System. It has a workflow that includes a touchscreen interface and integrated barcode scanner. Its reduced footprint provides up to six times the throughput per square foot of laboratory bench space.

BioFire

Breath test

The BreathID Hp Lab urea breath test system for H. pylori detection provides batch-test analysis for maximizing lab testing throughput. For initial active infection detection or confirmation of eradiation, the technology automates data input and batch analysis to reduce human error and simplify reporting.

Meridian Bioscience

Benchtop analyzer

The EasyRA is a fully automated benchtop clinical chemistry analyzer. This system allows clinical laboratories to screen for drugs of abuse in urine while also allowing healthcare providers to assess routine chemistry panels including CMPs, lipids and liver enzymes on a single analyzer.

Carolina Liquid Chemistries

Critical-care analyzer

The Stat Profile Prime Plus is a whole-blood critical-care analyzer that combines cartridge technology for sensors and reagents with non-lysing whole blood co-oximetry technology. The test menu includes pH, PCO2, PO2, Na, K, Cl, iCa, iMg, Glucose, Lactate, BUN, Creatinine, Hct, Hb, SO2%, CO-Ox, and estimated plasma volume calculation, with results in about one minute

Nova Biomedical

Chemistry Analyzer

The RX imola is a bench-top clinical chemistry analyzer that has a throughput of 400 photometric and up to 560 tests per hour including ISE. The test menu includes proteins, lipids, antioxidants, cardiac and diabetes testing. The system also features random access, STAT sampling and intuitive software functionality to boost productivity.

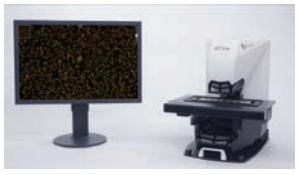
Randox

Automated assays

The Seegene analyzer performs a broad menu of molecular diagnostic tests in the areas of infectious diseases, women's health and personalized medicine. This includes the Allplex SARS-CoV-2/FluA/FluB/RSV Assay, which is pending submission and authorization from the U.S. Food and Drug Administration.

Seegene Technologies

Imaging system



The ZEUS dIFine Digital IF system is an IFA imaging and automated pattern recognition system. It allows users to analyze 96 HEp-2 wells in under an hour, including pinpointing the exact location of mitotic cells. The system performs positive/negative determination as it is scanning each well.

ZEUS Scientific

Automation solution

The Aptio Automation includes pre- and post-analytical modules that automate sample loading, preparation and handling. The portfolio of mid- and high-volume automation-ready analyzers also supports more than 800 clinical chemistry, immunoassay, hematology, and hemostasis tests and allows for interfaces to third-party analyzers.

Siemens Healthineers

CBC analyzer

The five-part CBC analyzer takes blood directly from a fingerstick or venous sample. OLO uses a disposable cartridge, eliminating the need for reagent management and maintenance. The analyzer comes factory calibrated for a quick set-up with minimal training. The CBC test is suitable for patients who are at least 3 months old.

Sight Diagnostics

Data upload feature

The PT Data Upload allows labs to upload their quantitative proficiency testing data, such as patient information, directly to WSLH, saving time and reducing manual data entry.

WSLH Proficiency Testing

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LABORATORY INNOVATOR

Helping Missouri labs through the pandemic

By Linda Wilson

Bill Whitmar, MS, is the Director of the Missouri State Public Health Laboratory, where he has held a variety of roles since 1989, including his first assignment in the breath alcohol program. He also is the President of the Association of Public Health Laboratories.

Will you describe what type of SARS-CoV-2 testing the Missouri State Public Health Laboratory (MSPHL) is doing?

The MSPHL offers rapid PCR testing utilizing assays from the Centers for Disease Control and Prevention (CDC) and TaqPath. The CDC assay was the first test used. We also offer serology testing for COVID antibodies, but the demand for that test within our laboratory has not been robust.

What are your daily testing totals and turnaround times?

In February and early March our daily specimen load was very low – typically in the single digits, but that steadily increased through the summer months to 200 per day. By the fall of 2020, our lab was testing as many as 800 specimens per day. Throughout these times, however, our turnaround time (TAT) has been 24 hours. We have maintained this TAT by acquiring additional high-throughput extraction devices and PCR instrumentation. We were also fortunate to be able to hire additional staff to accession specimens and test those specimens.

What steps has the MSPHL taken to help clinical labs throughout the state access equipment, supplies and other resources to facilitate testing for SARS-CoV-2?

We have been working with the Missouri labs, including those not on a state contract, to ascertain how to best accommodate their supply needs. Working with our state's emergency management agency, we utilize a website where labs enter an order for supplies and the support unit at the MSPHL fulfills and ships those orders the same day. To date, the MSPHL has shipped out nearly 500,000 tubes of media and 400,000 swabs to laboratories in Missouri. In addition, the lab has shipped out to hospitals and local public health agencies 9,500 vials of Remdesivir (mainly after hours to hospitals) and nearly 75,000 COVID test cartridges for the Abbott ID NOW rapid instrument.

The MSPHL laboratory director also has direct access to the regional resource representative at the Department of Health and Human Services. When a commercial or hospital laboratory finds itself in need of supplies or equipment that are back-ordered, the laboratory reaches out to me as the MSPHL laboratory director for assistance. I, in turn, receive the purchase order from the lab and send it on to the HHS representative and ask that the order be pushed up in the queue. That can be accomplished if the state is in what is termed a "red zone," or is in a state of high case counts or hospitalizations. More often than not, the back-ordered supplies or equipment will be received earlier using this method. Recently, plastics, like pipette tips, are in such short supply that this method has not achieved total success for orders with those supplies.

What lessons did MSPHL officials learn during the first wave of the pandemic and how are they applying those lessons going forward, particularly with the added complexity of flu season?

We should be ordering our supplies as a standing order, meaning we should receive supplies on a regular basis. We often do not receive as much as we order, but we do get some supplies, which allows us to get by.

In our lab we have numerous assays to consider with a multiplex flu/COVID, CDC COVID-only and then the assays for specific flu strains. Depending on what the clinicians request and what the health programs and the epidemiologists desire, it can present a confusing picture of which test should be run on a specimen. Adding to this picture is the continued shortage of plastic consumables. We can't just run a number of tests on each specimen anymore. We all have to have thoughtful use of our supplies.

Let us turn now to the role of the Association of Public Health Laboratories (APHL). What does the association see as its role during the COVID-19 pandemic and how is it fulfilling that role?

We have been working diligently to support our member laboratories throughout the pandemic response. This includes developing and sharing guidance, closely coordinating activities among federal, state, local and industry partners, advocating for greater investment to expand laboratory testing capacity and much more.

Will you briefly describe the Sara Alert system and COVID-19 data lake and how APHL and public health organizations are using these electronic tools to monitor and manage the COVID-19 pandemic?

Sara Alert is a real-time COVID-19 monitoring and reporting tool. It enables public health officials to enroll people who are ill or who are at risk of developing COVID-19. Those who enroll can enter their symptoms, which provides officials with real-time insights into the spread of disease and allows them to quickly and efficiently identify people requiring care, or for those who have developed COVID-19, alert them when it is safe to discontinue isolation. Sara Alert is hosted on the APHL Informatics Messaging Services (AIMS) platform, a secure, cloud-based environment.

APHL also has built and maintains a data lake on AIMS to help paint a comprehensive picture of the nation's testing landscape and needs. APHL originally developed the data lake for monitoring cases of antibiotic resistance, but with the emergence of COVID-19, APHL quickly reconfigured its data lake. It now holds nearly all the nation's COVID-19 testing data from public health departments.

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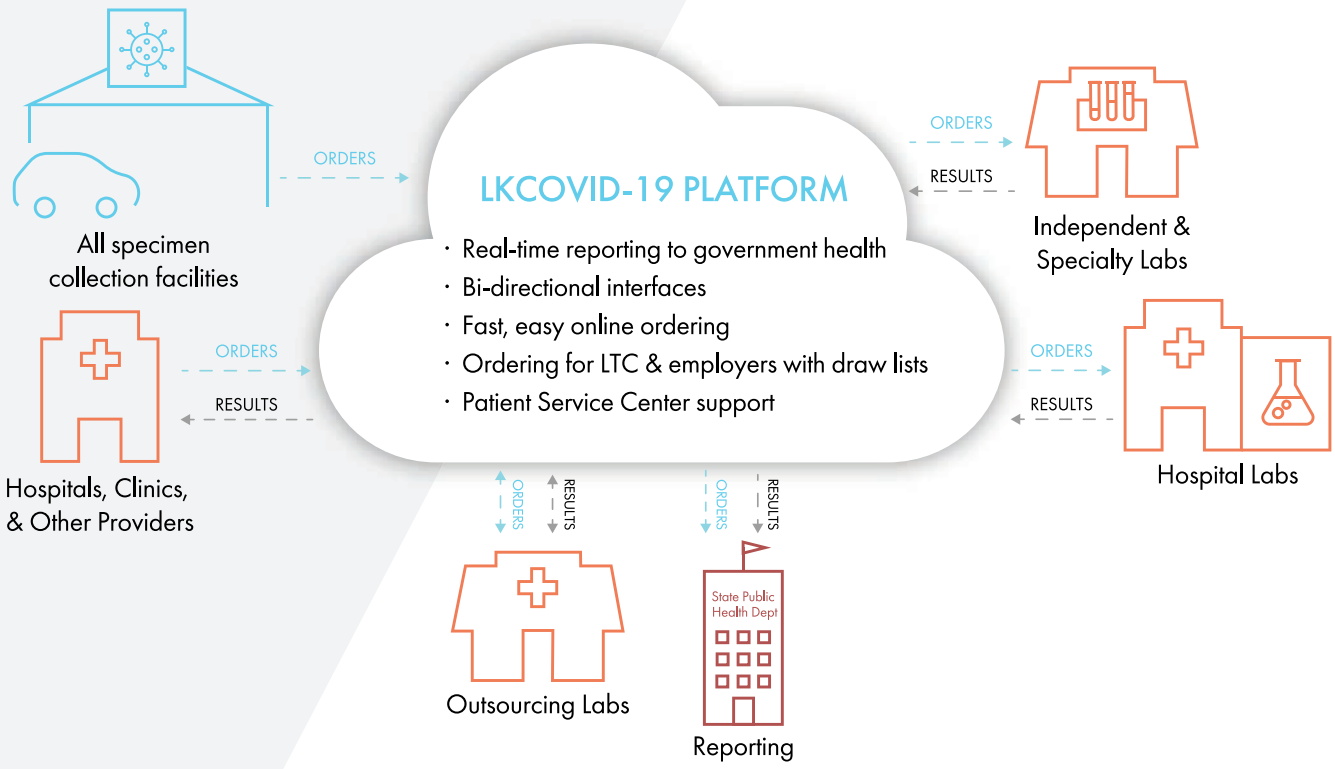

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