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NOVEMBER 2020 ▪ Vol 52 ▪ No 11

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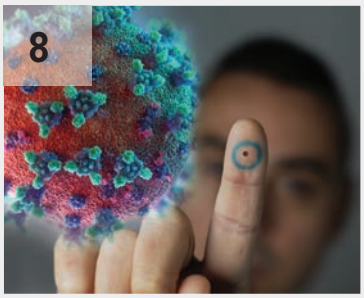

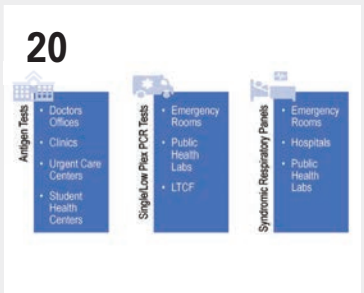

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The State of the Industry: MDx in 2020

By Brenda Silva
Senior Editor

As our calendar pages turn to the final months of the year, 2020 will be remembered for many occurrences that left lasting marks on the clinical laboratory industry, with nothing so memorable as the arrival of the SARS-CoV-2 virus and subsequent COVID-19 disease. From the first reports of an emerging infectious disease that affected thousands in Wuhan, China, at the end of December 2019, to the growth of global cases that began a rapid climb into the millions, COVID-19 made its presence and severity known with disease-related deaths that have now reached into the millions as well.

As a pandemic that conceivably had no historic equivalent in terms of its transmission speed and number of people affected – both of which still are still increasing – COVID-19 has also moved outside the lab and continues to permeate almost every aspect of daily living around the world. Businesses forced to operate remotely, classrooms that remain empty, and high-risk age groups separated from family are just a few examples of the influence of a disease that offers equal-opportunity infection for people who leave their homes.

For clinical laboratorians, the arrival of COVID-19 disrupted daily procedures and raised already-increased lab testing demands, which served to show how unprepared for a pandemic of COVID-19's magnitude many labs truly are. Lab managers realized that daily-use personal protection equipment (PPE) and testing supplies previously considered adequate were quickly depleted. They also had difficulty replacing the same items as manufacturers and suppliers struggled to keep pace with patient cases and testing demands.

Because of its pervasiveness in the lab and in the world, molecular diagnostic testing for COVID-19 was an easy choice for our final 2020 State of the Industry quarterly study. In selecting this topic for further research via a survey, *Medical Laboratory Observer (MLO)* asked our readers about how labs are handling increased testing demands, as well as issues with maintaining PPE and lab safety, and confidence levels in existing COVID-19 tests. Respondents were offered the opportunity to submit commentary on current COVID-19-related challenges facing the clinical lab, with follow-up replies that also looked at targeted areas that may need more attention in the future.

In looking to the near future, optimistic promises of ready-to-use vaccines linger in the air and in the lab. Clinical trials continue to move towards the finish line for five current vaccine candidates with U.S. government backing that are being tested and retested – much like the lab industry itself, in continually increasing lab testing demands. However, waiting at the finish line for the first successful vaccine is a group comprised of eager laboratorians, physicians and various governmental agencies who are anxious to put 2020 and COVID-19 behind them. They all stand ready for the next potential pandemic with more knowledge and hands-on expertise, both painfully gained over the course of the last year, to draw upon to meet the challenges new infectious diseases may present.

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

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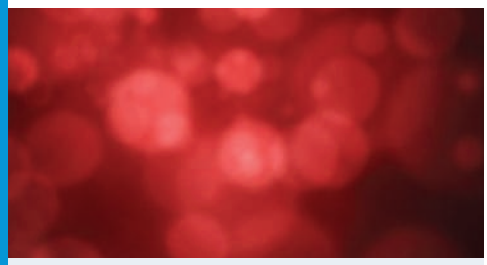


Fast Facts
Transfusion Medicine

Preliminary results (not posted online) from the 2019 National Blood Collection and Utilization Survey from the Centers for Disease Control and Prevention (CDC), as presented during AABB's annual meeting, shows stable pricing, a downward trend in the transfusion of plasma, and an upward trend in transfusion of platelets.

10,849,000
Is the total number of blood (whole blood and red blood cells) units transfused, up 1.8% since 2017, while 11,167,000 units were collected in 2019.

2,243,000
Is the total number of platelet units transfused, up 15.8% since 2017, while 2,348,000 units were collected in 2019.

2,185,000
Is the total number of plasma units transfused, down 8% since 2017, while 2,535,000 units were collected in 2019.

$208
Is the cost per unit of red blood cells, up $1 since 2017

$516
Is the cost per unit of platelets, down $1 since 2017

$50
Is the cost per unit of fresh frozen plasma, down $1 since 2017.

• **Source:** https://blog.aabb.org/the-2019-nbcus-shows-where-things-stand-in-blood-collection-and-use/

Study finds 100 percent death rate in COVID-19 patients after CPR

All 54 COVID-19 patients who underwent cardiopulmonary resuscitation (CPR) in a Michigan hospital died, leading to questions about the risks and benefits of performing a procedure that exposes healthcare personnel to the coronavirus amid limited supplies of personal protective equipment (PPE), according to a news report from the Center for Infectious Disease Research and Policy (CIDRAP) at the University of Minnesota.

The findings, published in a research letter in *JAMA Internal Medicine*, found that 52 of 54 patients who experienced cardiac arrest from March 15 to April 3 (96.3 percent) had non-shockable rhythms, 44 (81.5 percent) with pulseless cardiac electrical activity, and 8 (14.8 percent) with asystole (flatlining). Non-shockable rhythms are those in which the use of defibrillation is highly unlikely to restore a normal heartbeat.

Two patients (3.7 percent) had pulseless ventricular tachycardia (an abnormally fast heart rhythm). CPR achieved a return of spontaneous circulation (ROSC) in 29 patients (53.7 percent) after a median of 8 minutes. Of the 29 patients, 15 (51.7 percent) had their code status changed to do not resuscitate, and 14 patients (48.3 percent) were recoded and underwent additional CPR; all died.

Median time from hospital admission to cardiac arrest was 8 days, and median duration of CPR was 10 minutes. At cardiac arrest, 43 patients (79.6 percent) were receiving mechanical ventilation, 18 (33.3 percent) were on dialysis, and 25 (46.3 percent) required vasopressor drugs to treat low blood pressure.

Median patient age was 61.5 years, 33 of 54 patients (61.1 percent) were men, 36 (66.7 percent) were black, and many had obesity (median body mass index was 33 kg/m2), high blood pressure (42 patients, 77.8 percent), diabetes (50 [55.6 percent]), and high cholesterol (27 [50.0 percent]).

Model shows how COVID-19 could lead to runaway inflammation

A study from the University of Pittsburgh School of Medicine and Cedars-Sinai addresses a mystery first raised in March: Why do some people with COVID-19 develop severe inflammation? The research shows how the molecular structure and sequence of the SARS-CoV-2 spike protein – part of the virus that causes COVID-19 – could be behind the inflammatory syndrome cropping up in infected patients, according to a press release.

The study, published in the *Proceedings of the National Academy of Sciences*, uses computational modeling to zero in on a part of the SARS-CoV-2 spike protein that may act as a "superantigen," kicking the immune system into overdrive as in toxic shock syndrome – a rare, life-threatening complication of bacterial infections.

Symptoms of a newly identified condition in pediatric COVID-19 patients, known as Multisystem Inflammatory Syndrome in Children (MIS-C), include persistent fever and severe inflammation that can affect a host of bodily systems. While rare, the syndrome can be serious or even fatal.

The research team created a computer model of the interaction between the SARS-CoV-2 viral spike protein and the receptors on human T cells, the foot soldiers of the immune system. Under normal circumstances, T cells help the body fight off infection, but when these cells are activated in abnormally large quantities, as is the case with superantigens, they produce massive amounts of inflammatory cytokines – small proteins involved in immune system signaling – in what's known as a cytokine storm.

Using this computer model, the team was able to see that a specific region on the spike protein with superantigenic features interacts with T cells. Then they compared this region to a bacterial protein that causes toxic shock syndrome and found striking similarities in both sequence and structure. Importantly, the proposed SARS-CoV-2 superantigen showed a high affinity for binding T cell receptors – the first step toward touching off a runaway immune response. By finding protein-level similarities between SARS-CoV-2 and the bacterial structure that causes toxic shock syndrome, the researchers said they may have opened up new avenues for treating not only MIS-C patients, but also adults with COVID-19 infection experiencing cytokine storm.

Scientists discover genetic and immunologic underpinnings of some cases of severe COVID-19

New findings by scientists at the National Institutes of Health (NIH) and their collaborators help explain why some people with COVID-19 develop severe disease, according to a press release from the NIH. The findings also may provide the first molecular explanation for why more men than women die from COVID-19.

The researchers found that more than 10 percent of people who develop

severe COVID-19 have misguided antibodies – autoantibodies – that attack the immune system rather than the virus that causes the disease. Another 3.5 percent or more of people who develop severe COVID-19 carry a specific kind of genetic mutation that impacts immunity. Consequently, both groups lack effective immune responses that depend on type I interferon, a set of 17 proteins crucial for protecting cells and the body from viruses. Whether these proteins have been neutralized by autoantibodies or – because of a faulty gene – were produced in insufficient amounts or induced an inadequate antiviral response, their absence appears to be a commonality among a subgroup of people who suffer from life-threatening COVID-19 pneumonia.

These findings are the first published results from the COVID Human Genetic Effort, an international project spanning more than 50 genetic sequencing hubs and hundreds of hospitals. The effort is co-led by Helen Su, MD, PhD, a senior investigator at the National Institute of Allergy and Infectious Diseases (NIAID), part of NIH; and Jean-Laurent Casanova, MD, PhD, head of the St. Giles Laboratory of Human Genetics of Infectious Diseases at The Rockefeller University in New York.

The wide variation in the severity of disease caused by SARS-CoV-2, the virus behind COVID-19, has puzzled scientists and clinicians. SARS-CoV-2 can cause anything from a symptom-free infection to death, with many different outcomes in between. Since February 2020, Su and Casanova and their collaborators have enrolled thousands of COVID-19 patients to find out whether a genetic factor drives these disparate clinical outcomes.

The researchers discovered that among nearly 660 people with severe COVID-19, a significant number carried rare genetic variants in 13 genes known to be critical in the body's defense against influenza virus, and more than 3.5 percent were completely missing a functioning gene. Further experiments showed that immune cells from those 3.5 percent did not produce any detectable type I interferons in response to SARS-CoV-2.

Examining nearly 1,000 patients with life-threatening COVID-19 pneumonia, the researchers also found that more than 10 percent had autoantibodies against interferons at the onset of their infection, and 95 percent of those patients were men. Biochemical experiments confirmed that the autoantibodies block the activity of interferon type I.

Stroke patients with COVID-19 have increased inflammation, stroke severity and death

Stroke patients who also have COVID-19 showed increased systemic inflammation, a more serious stroke severity and a much higher rate of death, compared to stroke patients who did not have COVID-19, according to University of Alabama at Birmingham (UAB) research led by Chen Lin, MD, an assistant professor in the UAB Department of Neurology.

The research, published in *Brain, Behavior & Immunity – Health*, is a retrospective, observational, cross-sectional study of 60 ischemic stroke patients admitted to UAB Hospital between late March and early May 2020. Ischemic stroke occurs when a blood vessel for the brain is blocked by a clot, depriving some brain tissue of oxygen. All patients were tested for COVID-19 at admission.

The UAB researchers mined electronic medical records of confirmed stroke cases for information on age, gender and race; clinical variables; laboratory data, including complete blood counts, blood chemistry and coagulation tests; and outcomes, including death, length of hospital stay and condition at discharge.

The ratio of the number of neutrophils to the number of lymphocytes, or the NLR, as calculated from blood count data, served as an index of the systemic inflammatory response. While other researchers have associated NLR with COVID-19 disease severity, refractory disease and even as an independent factor for mortality, "our study is the first to associate the NLR in patients with COVID-19 and ischemic stroke and stroke severity," Lin said. Of the 60 hospitalized patients with acute systemic stroke, nine were positive for a COVID-19 infection.

The UAB research had four major findings. First, patients who were positive for COVID-19 presented with a more severe neurological deficit at admission, as measured by the National Institutes of Health (NIH) Stroke Scale, or NIHSS, score, which averaged 18.4. Second, all patients with an NIHSS score higher than 4 – including uninfected patients – had a significantly higher NLR than those with lower scores. The NIHSS is used to predict lesion size and gauge stroke severity. Third, patients with COVID-19 had an increased inflammatory response, including significantly higher neutrophil counts, lower lymphocyte counts and an increased NLR, compared with uninfected patients. Finally, stroke patients with COVID-19 had a significantly higher mortality rate – 44.4 percent, versus 7.6 percent for uninfected stroke patients.

Measures to prevent spread of SARS-CoV-2 may also mitigate flu

Following widespread adoption of community mitigation measures to reduce transmission of SARS-CoV-2, the percentage of U.S. respiratory specimens that tested positive for influenza decreased from more than 20 percent to 2.3 percent and has remained at historically low inter-seasonal levels, the Centers for Disease Control and Prevention (CDC) reported in its Morbidity and Mortality Weekly Report.

Data from Southern Hemisphere countries also showed little influenza activity, the CDC said.

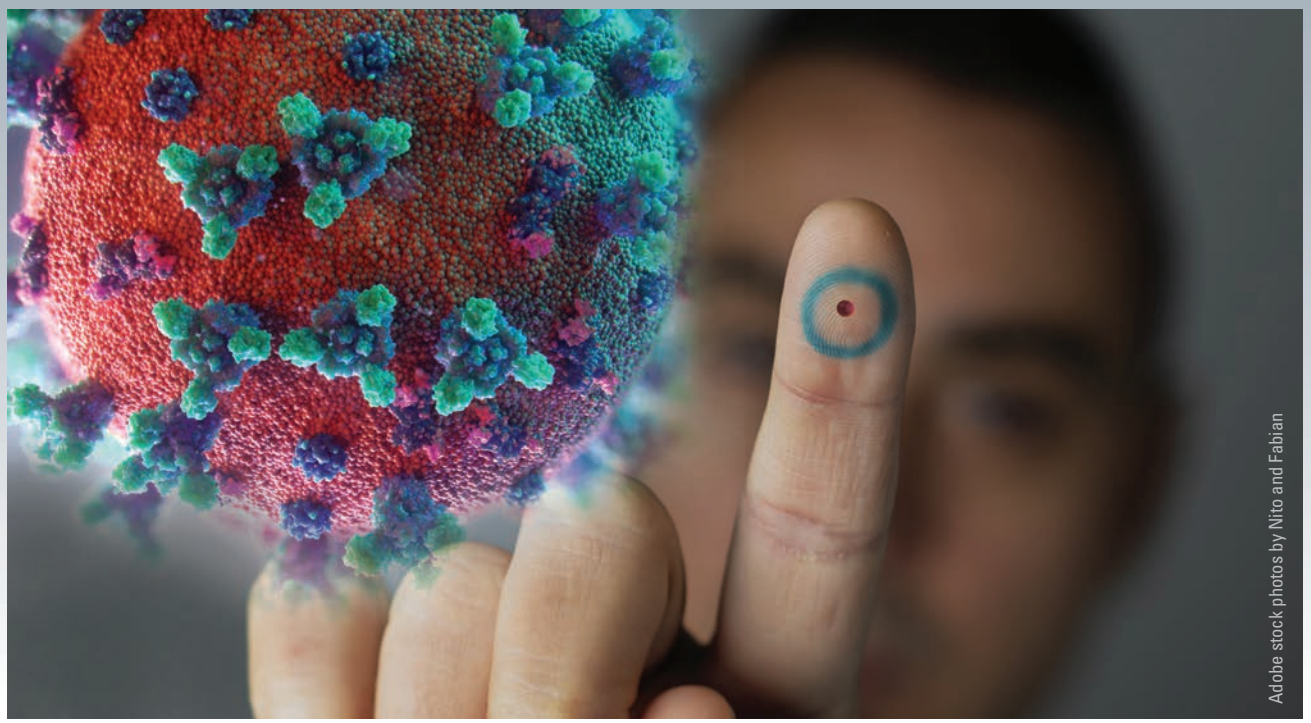
"These findings suggest that certain community mitigation measures might be useful adjuncts to influenza vaccination during influenza seasons, particularly for populations at highest risk for developing severe disease or complications," the CDC said.

After recognition of widespread community transmission of SARS-CoV-2, the virus that causes coronavirus disease 2019 (COVID-19), by mid- to late-February 2020, indicators of influenza activity began to decline in the Northern Hemisphere, the CDC reported.

Data from clinical laboratories in the United States showed a 61 percent decrease in the number of specimens submitted (from a median of 49,696 per week during September 29, 2019–February 29, 2020, to 19,537 during March 1–May 16, 2020) and a 98 percent decrease in influenza activity as measured by the percentage of submitted specimens testing positive (from a median of 19.34 percent to 0.33 percent). Inter-seasonal circulation of influenza in the United States (May 17–August 8, 2020) is currently at historical lows: a median of 0.20 percent positive tests in 2020, compared with 2.35 percent in 2019, 1.04 percent in 2018 and 2.36 percent in 2017, the CDC said.

During the period of April–July 2020, only 33 influenza positive test results were detected among 60,031 specimens tested in Australia, 12 among 21,178 specimens tested in Chile, and six among 2,098 specimens tested in South Africa, for a total of 51 influenza positive specimens among 83,307 tested in those countries.

"Although causality cannot be inferred from these ecological comparisons, the consistent trends over time and place are compelling and biologically plausible," the CDC said.



Hyperglycemia associated with hospitalization for severe COVID-19 infection

By Thomas P. Lohmann, MD, and Matthew C. Wagner, PhD

In December 2019, the novel Coronavirus 2019, also known as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), which causes COVID-19, began to rapidly spread around the globe. The total number of cases at this time is likely much greater than official diagnoses, as many may not know they are infected. Mild cases may be asymptomatic or experience vague symptoms, which patients do not consider severe enough to warrant testing, but these cases are still capable of transferring the virus to others, for whom the disease may be severe or even deadly.

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LEARNING OBJECTIVES

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

1. Describe the factors associated with increased risk of death from COVID-19.
2. Describe the evidence showing an association between diabetes, prediabetes and obesity and severe COVID-19.
3. Recall a confluence of factors linking hyperglycemia and the ACE2 pathway with severe COVID-19 infection.
4. Discuss the different types of assays for measuring HbA1c.

This highlights the necessity to find factors to determine the risk stratification of patients presenting with COVID-19 infections. This article will focus primarily on the risk factors of diabetes mellitus (DM) and uncontrolled hyperglycemia. It is important to acknowledge that diabetes is linked to comorbidities (such cardiovascular disease, renal insufficiency, and obesity) that are also risk factors for poor COVID-19 outcomes. There is growing evidence that the systemic pro-inflammatory state engendered by uncontrolled or poorly controlled diabetes and the related upregulation of Angiotensin Converting Enzyme II may be behind the increased severity of COVID-19 infections in these patients.

Once molecular testing for COVID-19 gave a more precise picture of the pandemic, it became clear that a subset of infected patients developed acute respiratory distress (ARDS), requiring hospitalization. Early reports from the outbreak in China identified the increased risk of death in these hospitalized patients,[1] and identified risk factors for hospitalization, including people over the age of 65, males, and those with comorbidities such as hypertension, diabetes, cardiovascular diseases and respiratory diseases. Subsequent publications included other population groups, including one that analyzed the health records of over 17 million individuals in Great Britain, and similarly found comorbidities associated with hospitalization and increased risk[2] of severe COVID-19 to include cardiovascular, respiratory, kidney, neurological, or liver disease, history of hematological malignancy or other recent cancer, autoimmune conditions, obesity, and diabetes. (The study also found

that Asian and Black demographics are at increased risk of death, which was only partially attributed to comorbidity, deprivation, or other risk factors.)

A U.S. study (compiled by the COVID-19 Associated Hospitalization Surveillance Network) similarly highlighted the importance of comorbidities in hospitalized US COVID-19 patients as summarized in **Table 1.**

Hyperglycemia

Among people with COVID-19 who require hospitalization, studies have found that many also have diabetes. For example, a recently published study involving 184 patients admitted to a New Jersey hospital for COVID-19 found that 85.9 percent had either diabetes mellitus (62.0 percent, HbA1c ≥6.5 percent) or prediabetes (23.9 percent, HbA1c =5.7-6.4 percent).[3] A further 4.3 percent of patients had a normal HbA1c, but a BMI >30 kg/m.[2]

The prevalence of diabetes in this patient group is 4.7 times higher than that of the general U.S. population, while the prevalence of prediabetes was 1.3 to 6.4 times higher. A significant number of patients were clinically obese, with a BMI >30 kg/m^2. Presumably, diabetic and non-diabetic individuals are as likely to be exposed to COVID-19, but some aspect of diabetes results in diabetics more frequently experiencing poor outcomes and requiring hospitalization.

The study also found that HbA1c levels measured at admission, taken as an indication of glycemic control over the prior nine to 12 weeks, were in the prediabetic range in 37.4 percent of patients, and in the range of a diabetes diagnosis in 48.0 percent of patients.[3] As outlined in **Table 2,** when sorted by age, COVID-19 patients 60 years old or younger were more likely to be clinically obese (65.3 percent) compared to those patients older than 60 years (26.6 percent). Similarly, COVID-19 patients 60 years old or younger had a significantly higher mean HbA1c than older patients (8.0 percent HbA1c vs 6.9 percent HbA1c, P=.003), suggesting more pronounced metabolic dysregulation in the younger hospitalized patients. Whereas the older hospitalized COVID-19 patients likely had many additional comorbidities, among the younger patients it appears that diabetes – and not just diabetes but uncontrolled or poorly controlled diabetes – is contributing to poor outcomes from the COVID-19 infection.

Common Comorbidities and frequency in US hospitalized COVID-19 Patients	
Hypertension	49.7%
Obesity	48.3%
Chronic lung disease	34.6%
Diabetes mellitus	28.3%
Cardiovascular disease	27.8%

Table 1.
Source: COVID-19 Associated Hospitalization Surveillance Network (COVID-NET)

Similar to initial hospitalization, the need for intubation can be taken as a further indicator of severity and

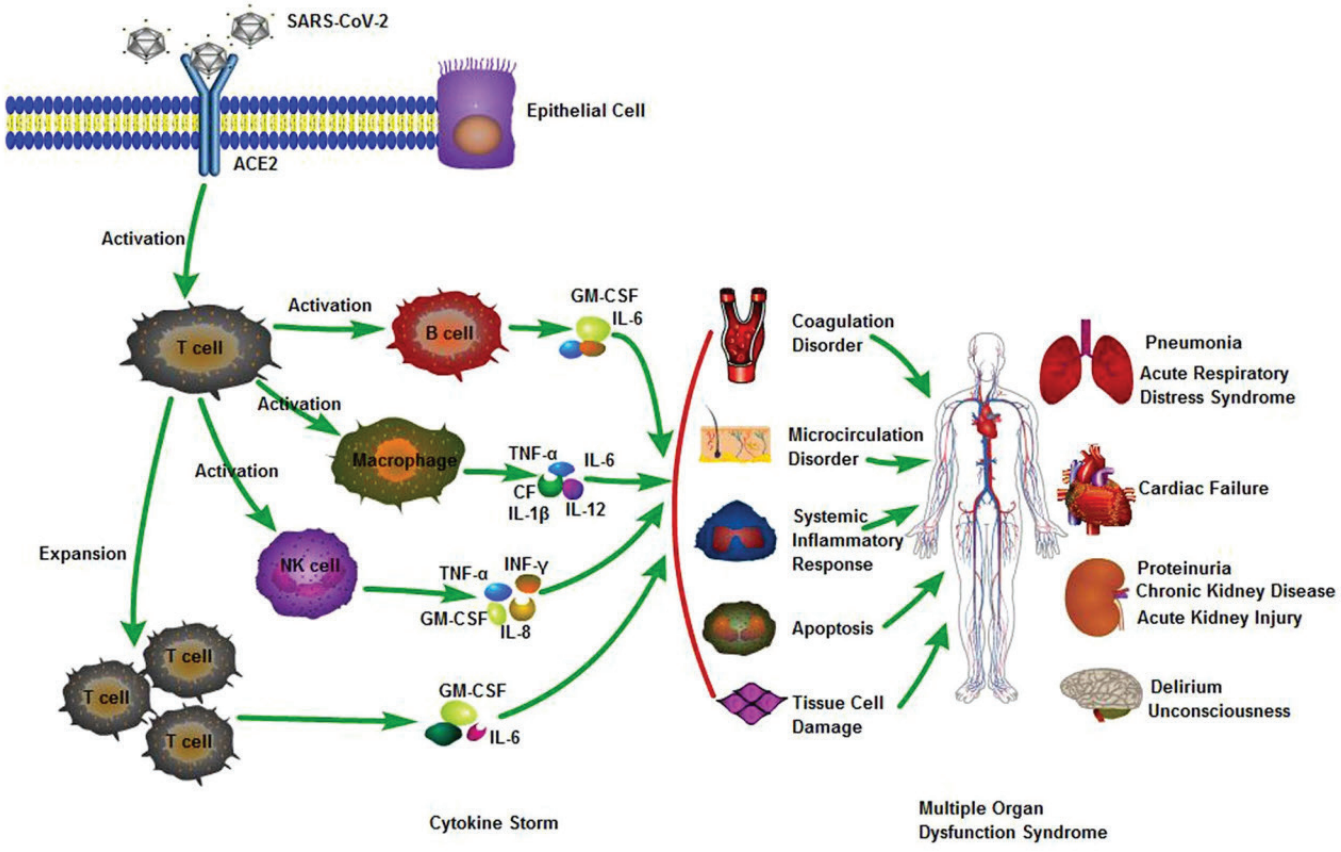

Figure 1.ACE2 Involvement in cytokine storm initiation
Source: Tong, T., Wu, Y., Ni, W. et al. The potential insights of Traditional Chinese Medicine on treatment of COVID-19. Chin Med 15, 51 (2020). https://doi.org/10.1186/s13020-020-00326-w

progression of COVID-19. The data about intubation continues to support the importance of glucose metabolism dysregulation in predicting COVID-19 severity. In the population of patients requiring intubation, 97.6 percent were either known diabetics or had elevated HbA1c, with the mean HbA1c being higher in the intubated group (8 percent HbA1c) than in the non-intubated group (7.2 percent HbA1c). Similarly, fasting blood glucose (FBG) at admission was elevated in the intubated group (238.0 vs. 163.7 mg/dl), and only one patient in the intubated group was categorized as non-diabetic, although in that case the patient was clinically obese. Some patients in the study population died without being intubated, and the majority were diabetic (70.9 percent), or prediabetic (16.7 percent).

Diabetes status, obesity rate, and HBA1c levels by age

	Patients ≤60 y (N = 75)	Patients >60 y (N = 109)	P value
DM (%)	64.0	60.6	.38
PreDM (%)	24.0	23.9	.50
NonDM (%)	12.0	15.6	.32
Mean FBG, mg/dL	200.5	165.4	.10
Mean BMI	33.4	27.2	<.0001
BMI >30 kg/m2	65.3	26.6	<.0001
BMI >40 kg/m2	20.0	3.7	.0004
HbA1C (%)	8.0	6.9	.003

Table 2.
Abbreviations: BMI, body mass index; DM, diabetes mellitus; FBG, fasting blood glucose; HbA1C, hemoglobin A1c; nonDM, nondiabetic; preDM, prediabetes. (Souce: See reference 3)

It should be noted that both pre-existing stress and the use of corticosteroids can cause increases in blood glucose, especially in severely ill hospitalized patients, which may complicate the interpretation of this data. However, of the 54 patients in this study classified as prediabetic, almost half had markedly elevated fasting blood glucose levels in the absence of glucocorticoid therapy. Additionally, six patients without known diabetes mellitus and a normal HbA1c on admission had repeatedly elevated fasting blood glucose levels.

In summary, all of these findings present a link between dysregulation of glucose metabolism and severe COVID-19 infections in a hospitalized population.[3] Hyperglycemia and obesity can be used to stratify the risk of an adverse event (requiring intubation or resulting in death).

Other lab abnomalities in hospitalized COVID-19 patients

What other laboratory assays could be useful in stratifying the risk of patients admitted to the hospital for COVID-19 infection? With severe COVID-19 infection, abnormal laboratory results may be caused by systemic immune damage from the inflammatory response. However, when measuring the immune response, many of the markers detectable by laboratory assay (such as elevation of: aspartate aminotransferase, serum creatinine, troponin, procalcitonion, lactate dehydrogenase, GGT) cannot be used to predict those patients that would require intubation or who would ultimately expire.

More interesting are the noted increases in the levels of inflammatory-related markers – such as C-reactive protein, serum ferritin, Erythrocyte sedimentation rate (ESR), Interleukin-6, and coagulation parameters such as D-dimer and Fibrinogen – that may be associated with the risk for severe COVID-19.[4]

These are interesting in the context of diabetes because type 2 diabetes is widely reported as either a chronic, low-grade inflammatory disease caused by long-term immune imbalance, or a metabolic syndrome associated with obesity. In the latter case, obesity is also linked to chronic inflammation, characterized by an increased abundance and activation of innate and adaptive immunity cells in adipose tissue, along with an increased release of inflammatory factors and chemokines both locally and systemically.[5] This connection draws a direct link between the increased risk of severe COVID-19 outcomes and chronic inflammation.

Scientists have independently hypothesized that COVID-19 induces a cytokine storm similar to that described in SARS (the viral outbreak first identified 2003). Type 2 diabetics – who would be more susceptible to the multi-organ failure resulting from such a cytokine storm due to their underlying chronic inflammation – would then be at greater risk of severe outcomes from COVID-19. This aligns well with the observations presented in the study above. Further, glucose dysregulation may lead to more severe COVID-19 infections by another mechanism, this time involving the entry of COVID-19 into host cells.

Angiotensin Converting Enzyme 2 (the cellular portal for COVID-19)

Of particular interest to COVID-19 infection is Angiotension Converting Enzyme 2, or ACE2. This enzyme – found in many organs including the lungs, heart, blood vessels, kidneys, liver, and GI tract – is part of the renin-angiotensin-aldosterone pathway, and plays a key role in regulation of blood pressure, wound healing and inflammation.

ACE2 acts in the body to convert Angiotensin II to inactive forms, which modulates the effects of this molecule responsible for increasing blood pressure and inflammation. Angiotensin II has, in particular, been linked to damage to blood vessel linings and various forms of tissue damage.

The severity of a particular COVID-19 infection could be explained by the factors influencing this pathway. Not only increased concentration of glycosylated SARS-CoV-2 viral particles in the lung epithelium, but increased concentration of glycosylated (reduced activity) ACE2 receptors in the lung epithelium may influence the degree and control of the pulmonary immune response to the SARS-CoV-2 spike protein at the key time frame of approximately day eight to 10 after symptom onset.

This is because, beyond ACE2's involvement in the inflammatory cascade, it appears to be the primary receptor for entry of SARS-CoV-2 into various epithelial tissues. (As a side effect, due to the high concentration of ACE2 in the tongue and oropharynx, infection by COVID-19 can be associated with loss of taste and smell during the acute infection.) The mechanism of viral entry into ACE2-containing cells is through an envelope-anchored spike protein. This allows entry of coronaviruses into host cells by binding to a host receptor and fusing viral and host membranes. Scientists believe that increases in glycosylation of both the viral spike protein, as well as ACE2 can enhance viral binding to ACE2 and the degree of the resultant immune

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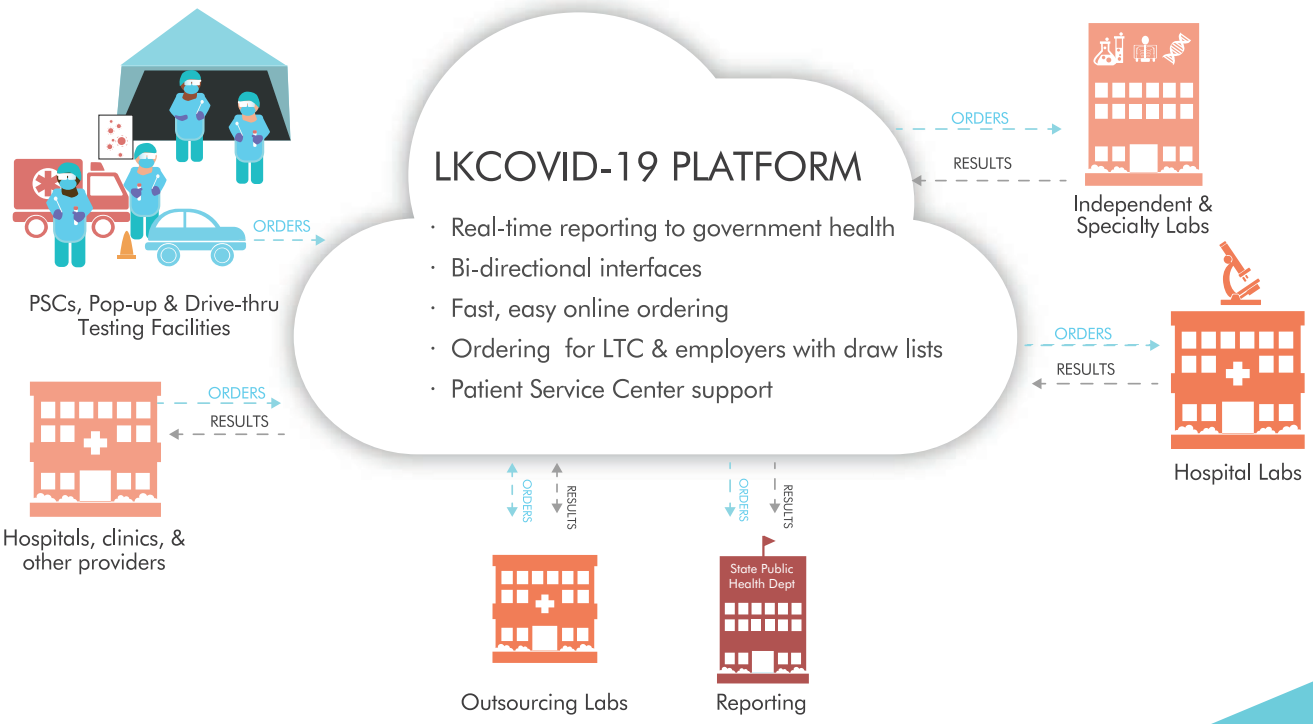

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response to the virus. This increased glycosylation is directly related to the patient's blood glucose level over the 10-12 days before the severe COVID-19 symptoms appear.[6]

Here we have found a confluence of factors linking hyperglycemia and the ACE2 pathway with severe COVID-19 infection. Not every patient presenting with hyperglycemia associated with COVID-19 has a history of diabetes mellitus, and many have a normal HbA1c on presentation. Instead, entirely apart from whether there is a prior history of diabetes, high fasting plasma glucose is an independent risk factor for morbidity and mortality. For those patients without prior diabetes and without steroid administration, hyperglycemia may result from initial viral infection of the pancreas and lungs, with loss of function of the endocrine (beta) cells of the pancreas, and resultant hyperglycemia.

This hyperglycemia results in upregulation of glycosylated ACE2 in the lungs, and further enhancement of viral binding to these glycosylated receptors. Notably, the glycosylated ACE2-receptors used as entry points by COVID-19 are then incapable of performing their regulatory action on Angiotensin II, further disabling the control of the inflammatory pathway.

As viral binding is thought to be enhanced by glycosylation of the ACE2 receptor, it is likely that the amount of glycosylated ACE2 receptor, and not simply the amount of ACE2 alone, is responsible for increased virus binding and fusion. If true, this argues for better glycemic control in patients with prediabetes and diabetes as a potential mechanism to slow COVID-19 spread and reduce the severity of symptoms, as better glycemic control should promote cellular pathways to downregulate the glycosylation of ACE2 receptors. Additionally, since 3.8 percent of the American population without a history of diabetes or prediabetes has a hemoglobin A1c over 6.1 percent in random sampling, use of high A1c as a risk stratification for COVID-19 could have merit.[6]

The use of HbA1c in the COVID-19 pandemic

Given the evidence suggesting that diabetes, prediabetes or obesity are risk factors for severe COVID-19, HbA1c is an important test for patients with suspected or confirmed SARS-CoV-2 infection. The evidence also supports rigorous screening of non-COVID-19 patients for diabetes or prediabetes because this will help providers know which patients would benefit from lifestyle changes that would lower their risk for severe COVID-19 should they become infected.

The groups of patients who would benefit from HbA1c testing are:

- Patients with symptomatic COVID-19 infection. Many patients with respiratory distress due to COVID-19 have HbA1c included in their admission laboratory orders. In patients with hyperglycemia, an increased HbA1c would indicate that the patient has had an increased glucose for a time predating the acute viral infection, and that these patients should be classified as unrecognized diabetics now infected by COVID-19, with the highest risk of complications from the infection. Patients presenting with HbA1c between 5.7-6.4 percent and hyperglycemia, are prediabetic, with an intermediate risk. Patients with hyperglycemia and a normal HbA1c would be non-diabetic patients presenting with high blood sugar, and with a lower associated risk of morbidity and mortality. Note that patients from the latter two categories (prediabetic and normal HbA1c with hyperglycemia) should have periodic HbA1c monitoring after discharge to detect progression to diabetes mellitus after recovery from the COVID-19 infection.
- Asymptomatic patient populations. This screening would be undertaken to detect patients in the prediabetic or unrecognized diabetic categories. Patients identified as either prediabetic or diabetic would benefit from lifestyle changes designed to reduce body mass index through enhanced exercise and dietary improvements. They could also be screened for associated comorbidities associated with adverse outcomes. Patients who subsequently become symptomatic for COVID-19 would already be aware of their diabetic state and whether they are at increased risk for a severe disease course.[7]

Further benefits may be gleaned from HbA1c screening of both symptomatic and asymptomatic populations. Some methods employed for the measurement of HbA1c, incidentally detect hemoglobin variants and thalassemias in patient populations. In particular, the detection of Hemoglobin S (alone or in combination with other common Hb variants D,C,E or thalassemia) is of great importance, as the Centers for Disease Control and Prevention (CDC) has issued guidance that individuals with sickle cell anemia or thalassemias are at increased risk of developing severe COVID-19 infection.[8]

For a patient presenting with acute respiratory compromise and who will have HbA1c testing done, it is also important to consider the testing environment. At presentation, the HbA1c testing will likely be performed without access to prior laboratory records. Screening of

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Learning Objectives

- Understand the prognostic significance of electrolyte abnormalities in COVID-19
- Identify key electrolyte abnormalities in advanced COVID-19 illness and recommendations for monitoring and treatment
- Understand frequency and pathophysiology of acute kidney injury in COVID-19 illness
- Identify strategies to manage AKI in an acute care setting

Educational Credits

This program has been approved by the American Association of Critical-Care Nurses (AACN), for 1.00 CERPs, Synergy CERP Category A, File Number 23381. Approval refers to recognition of continuing education only and does not imply AACN approval or endorsement of the content of this educational activity, or the products mentioned.

Presenter:

Dennis Begos, MD, FACS, FACRS
Associate Medical Director, Medical and Scientific Affairs, Nova Biomedical

Prior to Nova, Dennis was in clinical practice as a surgeon for over 20 years. After finishing medical school at New York Medical College, he did his general surgery residency at Yale and a fellowship in colorectal surgery at the Cleveland Clinic. He was an assistant professor at Tufts University School of Medicine, and also practiced at Winchester Hospital in Massachusetts. He was Chair of the Department of Surgery and President of the medical staff at Winchester Hospital. He has always been heavily involved in medical education in addition to his clinical practice and won numerous teaching awards from Tufts. He has been a reviewer for several surgical journals and has published numerous peer-reviewed articles and book chapters.

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asymptomatic populations that have no specific history of diabetes mellitus will also likely be reviewed in isolation. In these settings, the American Diabetes Association (ADA) has suggested that the method chosen for HbA1c testing allow for the determination of a clinical condition that may affect the red cell circulating lifespan, such as homozygous or doubly-heterozygous hemoglobinopathies or thalassemias.[9]

Why is this important? The HbA1c assay is used as an estimate of the average glucose concentration (AGC) over the past nine to 12 weeks. The proportional relationship between HbA1c and AGC assumes that the patient's hemoglobin molecules are exposed to glucose over a normal red blood cell (RBC) lifespan. Conditions that reduce the survival of circulating RBC's will reduce the patient's HbA1c in relation to the degree of reduction in red cell survival. Therefore, the detection of some of the more common causes of decreased (or increased) RBC survival would be important in determining whether the HbA1c level was an accurate reflection of a patient's level of glycemic control.

Hemoglobinopathies or thalassemias may be clinically silent but may cause reductions in red cell circulation time. The ADA recommendation is key to correctly identify those patients who are without proper glycemic control, but where the condition is incidentally concealed by the patient's hemoglobinopathy. In the current situation, we are similarly concerned with correctly spotting a COVID-19 patient with a significant comorbidity that may be concealed by a hemoglobinopathy, and also incidentally discovering the hemoglobinopathy, which itself may be a risk factor for severe COVID-19 infection.

Methods of analyzing HbA1c fall into two categories:

- Separation methods, such as high-performance liquid chromatography (HPLC) and capillary electrophoresis. These methods may incidentally detect many hemoglobinopathies and thalassemias for later confirmation.
- Non-separation methods, such as immunoassay, enzymatic cleavage, or boronate affinity chromatography. These are incapable of noting when hemoglobin variants or thalassemias are present, but they can be used if the patient's prior results do not indicate the presence of a hemoglobinopathy or other disease state that can alter the RBC lifespan.

Clearly, methods capable of detecting (and appropriately flagging) the presence of abnormal hemoglobin molecules would allow the performing laboratory to notify the ordering clinician of an abnormality in the HbA1c trace. The clinician would then know that the reported HbA1c value may not reflect the patient's average glucose concentration over the past 12 weeks. A falsely low HbA1c, if unrecognized, could classify a diabetic patient as being normo-glycemic in error.

It is advisable that the method chosen for screening give information related to the presence of hemoglobin abnormalities, and that with homozygous or double heterozygous conditions, an alternate test be chosen for screening.[9] This is particularly important when testing acutely ill patients presenting with acute respiratory distress when no prior medical chart is available, or in screening programs looking for prediabetic or previously unknown diabetic patients in the general population in an effort to identify at-risk individuals.

Summary

Early in the COVID-19 pandemic, it was recognized that certain subsets of hospitalized patients had poorer outcomes, based on patient age, body mass index, and comorbidities. This review focused on the presence of hyperglycemia as an independent risk factor. The role of glycation of the ACE2 receptor as an enabler of COVID-19 binding, and the increased risk of immunologic storm due to underlying chronic inflammatory state was discussed. Expanding upon this connection, HbA1c testing at hospital presentation can be used for risk stratification of hyperglycemic patients.

Additionally, the authors suggest screening of asymptomatic patients to detect prediabetes and previously unknown diabetes mellitus, which could be useful in intiating lifestyle changes to reduce these patients' risk of adverse events related to COVID-19. The choice of method for HbA1c screening should allow for an estimation of conditions that could artificially lower the HbA1c value, which could result in prediabetics or unknown diabetics being falsely classified as euglycemic.

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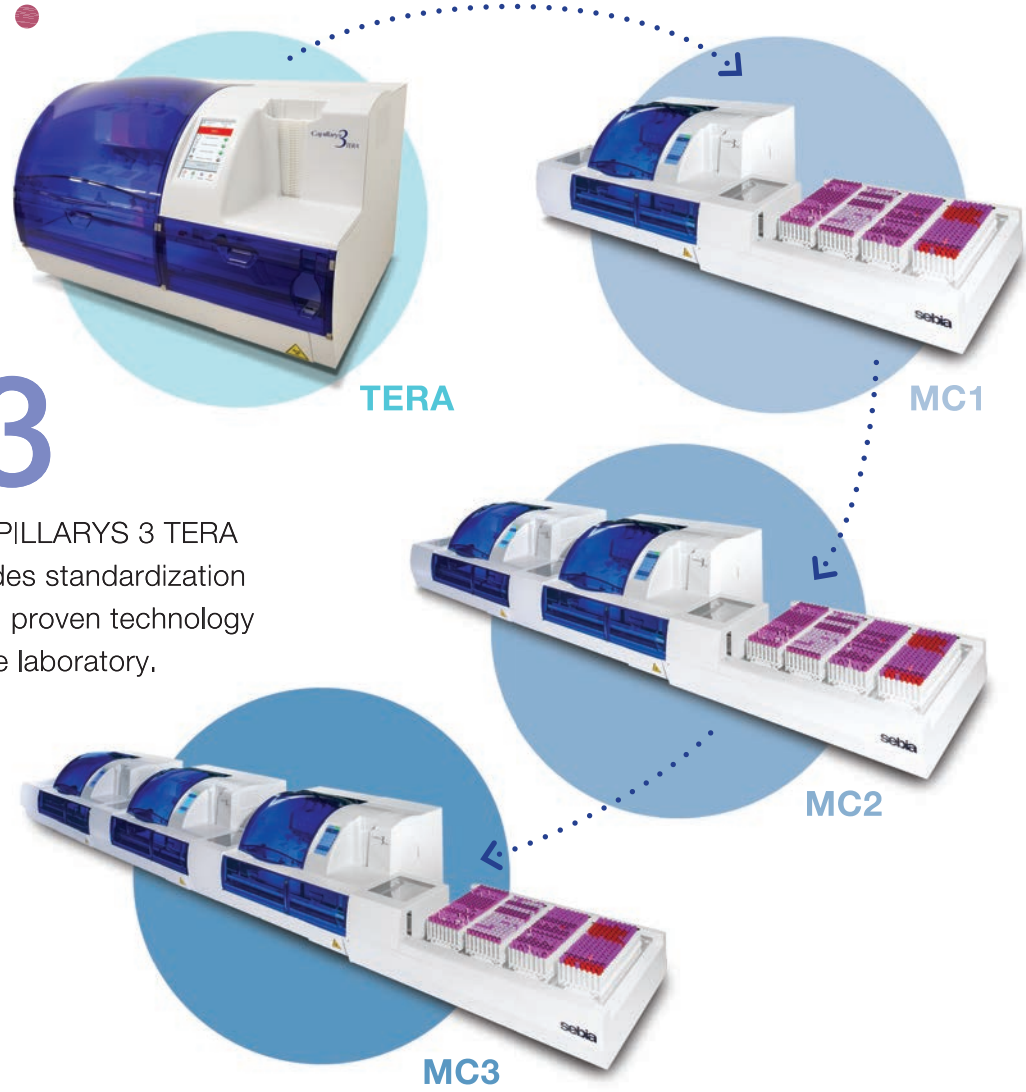

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CONTINUING EDUCATION TEST

Hyperglycemia associated with hospitalization for severe COVID-19 infection

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TEST QUESTIONS

Circles must be filled in, or test will not be graded. Shade circles like this: ● Not like this: Ⓧ

1. **Some of the identified risk factors for increased likelihood of death in COVID-19 patients included people over the age of 65, males and those with comorbidities such as hypertension,_____, cardiovascular diseases and_____.**
   - A. diabetes, seasonal allergies
   - B. diabetes, respiratory diseases
   - C. respiratory diseases, hypotension
   - D. hypotension, diabetes

2. **A recently published study involving 184 patients admitted to a New Jersey hospital for COVID-19 found that 85.9 percent had either diabetes mellitus (62 percent, _____) or prediabetes (23.9 percent, _____).**
   - A. HbA1c ≥6.5 percent; HbA1c =5.7-6.4 percent
   - B. HbA1c ≥ 10 percent; HbA1c=5.7-6.4 percent
   - C. HbA1c. ≥ 6.5 percent; HbA1c=6.0-7 percent
   - D. HbA1c≥ 4.0 percent; HbA1c=5.0-6.0 percent

3. **A significant number of patients in the prediabetic or diabetic group were clinically obese, with a _____.**
   - A. BMI > 25kg/m^2
   - B. BMI > 30kg/m^2
   - C. BMI > 35kg/m^2
   - D. BMI > 40kg/m^2

4. **Patients less than or equal to 60 years old were more likely to be clinically obese (65.3 percent) compared to those patients older than 60 years.**
   - A. True
   - B. False

5. **In the population of patients requiring intubation, 97.6 percent were either known diabetics or had elevated HbA1c, with the mean HbA1c being higher in the intubated group (___ percent HbA1c) than in the non-intubated group (___ percent HbA1c).**
   - A. 8; 7.2
   - B. 6, 7.2
   - C. 5; 8.1
   - D. 5; 7.2

6. **What two factors can complicate the interpretation of the data in severely ill hospitalized patients with increased blood sugar?**
   - A. beta blockers and corticosteroids
   - B. acetaminophen and pre-existing stress
   - C. pre-existing stress and corticosteroids
   - D. acetylsalicylic acid and beta blockers

7. **Increases in the levels of inflammatory-related markers – such as C-reactive protein, serum ferritin, Erythrocyte sedimentation rate (ESR), _____, and coagulation parameters such as D-dimer and Fibrinogen – may be associated with the risk for severe COVID-19**
   - A. serum creatinine
   - B. procalcitonion
   - C. Interleukin-6
   - D. GGT

8. **Type 2 diabetes is widely reported as a chronic, high-grade inflammatory disease caused by short-term immune imbalance, or metabolic syndrome associated with obesity.**
   - A. True
   - B. False

9. **Type 2 diabetics would be more susceptible to the multi-organ failure resulting from such a cytokine storm due to their underlying chronic _____.**
   - A. inflammation
   - B. hypotension
   - C. obesity
   - D. hypertension

10. **ACE2 – found in many organs including the lungs, _____, blood vessels, ___, liver, and GI tract – is part of the renin-angiotensin-aldosterone pathway.**
    - A. kidneys; brain
    - B. brain; GI tract
    - C. heart; kidneys
    - D. brain; bladder

11. **ACE2 receptors in the lung epithelium may influence the degree and control of the pulmonary immune response to the SARS-CoV-2 spike protein at the key time frame of approximately day 8 to 10 after symptom onset.**
    - A. True
    - B. False

12. **Beyond ACE2's involvement in the inflammatory cascade, it appears to be the primary receptor for entry of SARS-CoV-2 into various ____tissues.**
    - A. connective
    - B. muscle
    - C. nervous
    - D. epithelial

13. **The mechanism of viral entry into ACE2-containing cells is through an envelope-anchored _____ protein.**
    - A. membrane
    - B. envelope
    - C. nucleocapsid
    - D. spike

14. **For patients without prior diabetes and without steroid administration, hyperglycemia may result from initial viral infection of the pancreas and _____.**
    - A. heart
    - B. lungs
    - C. brain
    - D. GI tract

15. **Given the evidence suggesting that diabetes, prediabetes or obesity are risk factors for severe COVID-19, _____ is an important test for patients with suspected or confirmed SARS-CoV-2 infection.**
    - A. d-dimer
    - B. serum ferritin
    - C. HbA1c
    - D. GGT

16. **Patients with _____ and a normal HbA1c would be non-diabetic patients presenting with high blood sugar, and with a lower associated risk of morbidity and mortality.**
    - A. hypoglycemia
    - B. elevated LDL cholesterol
    - C. elevated potassium
    - D. hyperglycemia

17. **The Centers for Disease Control and Prevention (CDC) has issued guidance that individuals with _____ or thalassemias are at increased risk of developing severe COVID-19 infection.**
    - A. sickle cell anemia
    - B. Huntington's Disease
    - C. seasonal allergies
    - D. Down syndrome

18. **Conditions that reduce the survival of circulating _____ will reduce the patient's HbA1c in relation to the degree of reduction in _____ survival.**
    - A. red blood cells; red cell
    - B. white blood cells; white cell
    - C. red blood cells; white cell
    - D. white blood cells; red cell

19. **Diseases such as hemoglobinopathies or thalassemia may be clinically silent but may cause reductions in ____ circulation time.**
    - A. plasma
    - B. platelets
    - C. white cell
    - D. red cell

20. **Methods of testing for HbA1c that may also detect hemoglobinopathies and thalassemias include:**
    - A. capillary electrophoresis and high-performance liquid chromatography
    - B. immunoassay and capillary electrophoresis
    - C. enzymatic cleavage and immunoassay
    - D. boronate affinity chromatography and high-performance liquid chromatography

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The right test at the right time during the SARS-CoV-2 pandemic

By Adam Thornberg, MHS

The SARS-CoV-2 pandemic has had a grip on the world since the virus first appeared in December of 2019. Months later, professionals across the scientific and medical community have had to endure challenges that they may not have faced in their careers before now. With these new challenges come new ways of thinking and approaching different facets of the clinical cascade when caring for patients with COVID-19. Many countries have had to adapt their clinical practices to ever-changing guidelines, therapies, and approaches to the standard of care in order to help patients with a range of ailments.

As the pandemic has forged through 2020, the knowledge gap has begun to close, helping the medical and scientific community better care for patients with different levels of infection. This gap may be widened again when the pandemic collides with the upcoming respiratory season, which presents many unknowns.

In March of 2020, when much of the United States went into lockdown due to the pandemic, one thing became clear: the incidence of influenza cases declined sharply in just a few weeks.[1] However, during a nationwide lockdown where many additional precautions were in effect (i.e. mask-wearing, physical and social distancing) this could have been expected. With the 2020/2021 respiratory illness season on the horizon, while the world continues to experience increasing SARS-CoV-2 case counts, the United States, along with many other countries, is preparing for what might be an arduous season of respiratory illness in the face of pandemic fatigue.

Given that clinical laboratories have grappled with testing for SARS-CoV-2 throughout the pandemic, questions arise about what to do when other pathogens, especially influenza, begin to circulate again during the winter months. Labs have had to focus on testing for SARS-CoV-2 for months, bringing on multiple testing platforms and adding new tests onto existing platforms to keep up with testing demand. What this will mean as far as testing needs for influenza and other respiratory pathogens (e.g. rhinovirus) is still a blurry picture. Clinical laboratories and medical teams face even further challenges in the wake of economic reopening, which includes children and young adults returning to schools and colleges.

During a normal season of respiratory illness, influenza, or the flu, is a common household term. The incidence generally remains high year-over-year, despite the availability of antivirals and an influenza vaccine. Previously, any set of signs and symptoms may have been referred to as the flu, or maybe even just a cold if the symptoms were not as severe, but now the ramifications of not knowing the underlying cause of the infection could be much greater. The likelihood that an illness is either the flu or a cold is certainly plausible, but clinians should consider identifying the other pathogens, especially when a SARS-CoV-2 or influenza test result turns up negative.

The importance of testing for other respiratory pathogens

Other respiratory pathogens, which may have been dormant from the tail end of the winter through the summer, now have the opportunity to start circulating again. All the while, SARS-CoV-2 has not appeared to be seasonal – at least thus far.

When it comes to respiratory infections, it may be more important than ever during this season to understand when the etiology of infection is SARS-CoV-2 but also whether other important respiratory agents are playing a role in transmission and infection. The clinical presentation of respiratory infections and most of the symptoms a person may experience are widely similar, complicating diagnosis in the absence of a SARS-CoV-2-positive result, especially for those patients with underlying comorbidities.

Outside of influenza and SARS-CoV-2 lies a full spectrum of viruses and bacteria that cause acute upper respiratory tract infections. For example, another widely known virus, respiratory syncytial virus (RSV), has been associated with mortality rates up to 60 percent in untreated immunocompromised individuals. Although more commonly seen in the pediatric population, RSV has also caused severe outcomes in immunocompromised adults, especially the elderly and certain comorbidities could lead to a significant increase in the risk of hospitalization.[2] Furthermore, identifying the subtype of RSV as A or B could be of significance. Laham et al., for example, described a handful of studies where RSV A had propagated worse clinical outcomes in pediatric patients. In their study, RSV A had a higher severity of illness when certain confounding factors, like co-infection with another respiratory pathogen, were removed.[3]

Parainfluenza (PIV) has also been known to affect multiple age groups, with the more distressing cases of disease severity in younger children, older adults, and immunocompromised individuals. Lung and stem cell transplant recipients are a particularly high-risk population for infection with PIV. Each serotype has the potential to produce specific clinical symptoms and can be found circulating at different times throughout the year, making them a cause for concern both in and out of the common high-circulation months for most respiratory pathogens. Recent findings have shown that in immunocompromised adults, hospitalized adult pneumonia cases caused by PIV were associated with comorbidities, like chronic lung or heart disease. The importance of identifying this pathogen and its different serotypes could play a role for the clinical team in managing adult or pediatric patients, as PIV-3 has been seen to be more prevalent over PIV-1 and PIV-2 and has been associated with critical diseases including pneumonia and bronchiolitis.[4]

Since the 2003 coronavirus outbreak, which caused severe acute respiratory syndrome (SARS), the four common human coronaviruses (229E, HKU1, NL63, and OC43) have not received much publicity. However, these coronaviruses hold the ticket to 15-30 percent of respiratory tract infections each year, causing more severe infections in neonates, the elderly, and those with underlying conditions.[5] The other two well-known coronaviruses, SARS-CoV and Middle East Respiratory Syndrome Coronavirus (MERS-CoV), are recognized for their above average mortality rates, although only MERS-CoV is still circulating.

Rhinovirus is another contender. With over 100 serotypes, it may account for up to one-third of "common cold" cases. While healthy individuals generally may not suffer a great disease burden from rhinoviruses, other individuals like those in long term care facilities may be at an increased risk for poor outcomes. Louie et al. described a rhinovirus outbreak between two long

term care facilities in California, resulting in an attack rate of 100 percent and a mortality rate of 21 percent, with all the deaths being directly attributed to the acute infection.[6] Human metapneumovirus (hMPV) wreaked similar havoc in skilled nursing facilities in 2013, where the viral etiology was originally thought to be influenza. There was a total of 57 cases of upper respiratory tract infection, which were all caused by hMPV, and 11 percent of the patients at the two facilities died.[7]

Adenoviruses can be of particular concern for group settings as well. A recent outbreak that made news headlines occurred at the Wanaque Center for Nursing and Rehabilitation. During the time of the outbreak, a total of 36 children and 1 staff member were infected with adenovirus type 7, which has been linked to poor outcomes in patients with weakened immune systems. The adenovirus spread resulted in 11 untimely pediatric deaths.[8] Likewise, enteroviruses (EV) have been linked to poor outcomes in children. The viruses can cause not only upper respiratory tract infection but also lead to acute flaccid myelitis (AFM), which can rapidly progress to poor outcomes including paralysis and/or complications of respiratory failure that can be life-threatening even in healthy children. The most recent guidance from the Centers for Disease Control and Prevention (CDC) said that 2020 may be another peak year for AFM, as EV-D68 has circulated every two years between August and November since 2014 and is likely associated with a peak in AFM cases during these periods. The 2018 season highlights the importance of diagnostic testing for EV, as most children with limb weakness had a fever and/or respiratory illness before onset.[9]

While many more viruses can cause upper respiratory illness, viruses are not the only offenders causing varying levels of respiratory distress. Bacteria, such as *Chlamydia pneumoniae* and *Mycoplasma pneumoniae*, also play a role in atypical, community-acquired pneumonia with symptoms consistent with infections caused by some of the viruses previously described. The difference with these pathogens is that an antibiotic prescription is recommended for treatment in any population. Individuals with asthma or atopic disease that may have a less than optimal ability to produce an immune response, for example, have a substantial foe in *M. pneumoniae*, which has evolved to induce long-lasting infection.[10]

The clinical implications for co-infections do not appear to be widely studied and leave a bit of a knowledge gap, but we do know based on some studies that co-infections are a possibility with and without SARS-CoV-2 infection. Researchers from Stanford University School of Medicine recently published a research letter in *JAMA* detailing the prevalence of SARS-CoV-2 and other circulating respiratory pathogens, based on results from SARS-CoV-2 testing and a syndromic multiplex respiratory panel with targets spanning many different viruses and bacteria (See **Figure 1**). The authors found that infection with SARS-CoV-2 could not predict the presence or absence of another respiratory pathogen, which could have important implications for the upcoming respiratory season.[11] Another recently published study by Mandelia et. al., noted that viral co-infection epidemiology has been poorly understood, in general, even before the pandemic. However, of the samples that tested positive in their study, 10.8 percent were positive for more than one virus, with the pediatric patient population carrying a larger burden of co-infections and adenovirus being the most prevalent co-detected pathogen.[12]

The etiology of a respiratory tract infection can be challenging to differentiate clinically. Infections with one or more pathogens generally cannot be diagnosed by symptoms only, further complicating patient management and treatment. Being able to identify

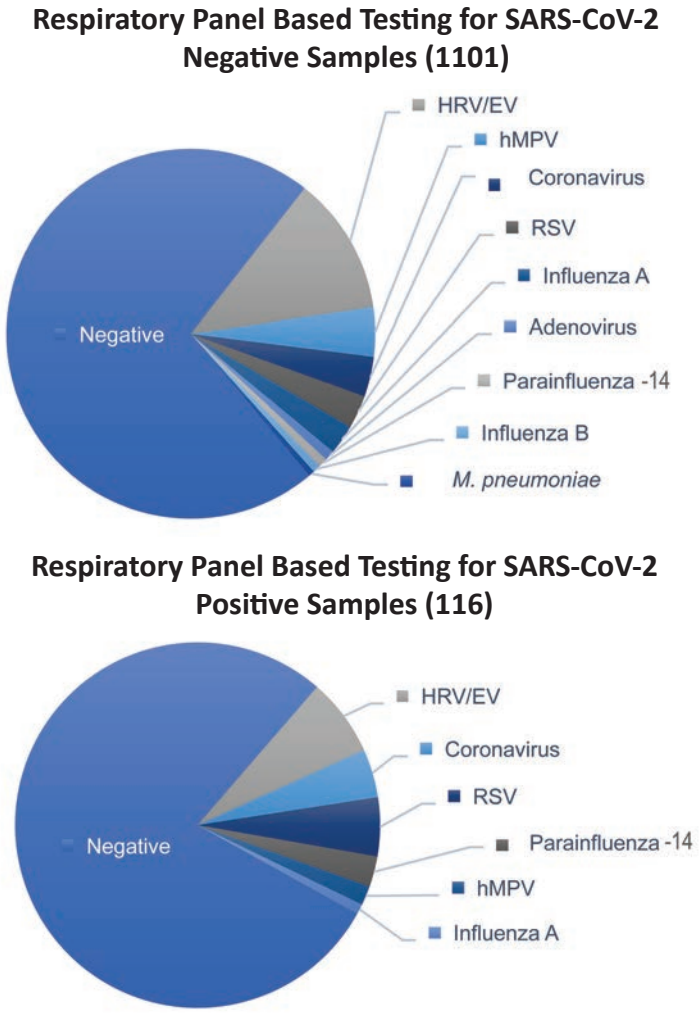

Figure 1. Prevalence of Respiratory Pathogens in Samples that Tested Positive or Negative for SARS-CoV-2 (Source: see reference 11)

the causative agent(s) in an upper respiratory tract infection can be useful information in the clinical management of any patient. With the inability to predict how effective the influenza vaccine will be over a specific flu season, determining whether a patient has been infected with influenza will be key to properly prescribing an antiviral in the appropriate timeframe. Likewise, if a bacterial pathogen is detected, an antibiotic might need to be administered to help curb the infection. Given that there are no other widely disseminated treatments for other viral pathogens, prescription of an antiviral or antibiotic likely will be given preemptively or under clinical suspicion when it may not be needed.

Combating antimicrobial resistance

While much of the public has been focused on the pandemic, the scientific and medical community has not forgotten about the major burden of antimicrobial resistance (AMR) worldwide. A recent Clinical and Laboratory Standards Institute News Update explored what we know about AMR during the COVID-19 pandemic, including the widespread use of antibiotics for presumed or confirmed secondary bacterial infections, and what the clinical microbiology lab can do to help prepare for the AMR pandemic with key activities.[13]

One of the suggestions that the authors in the update made is for the rapid detection of respiratory pathogens, which can be done using syndromic multiplex molecular respiratory panels.[13]

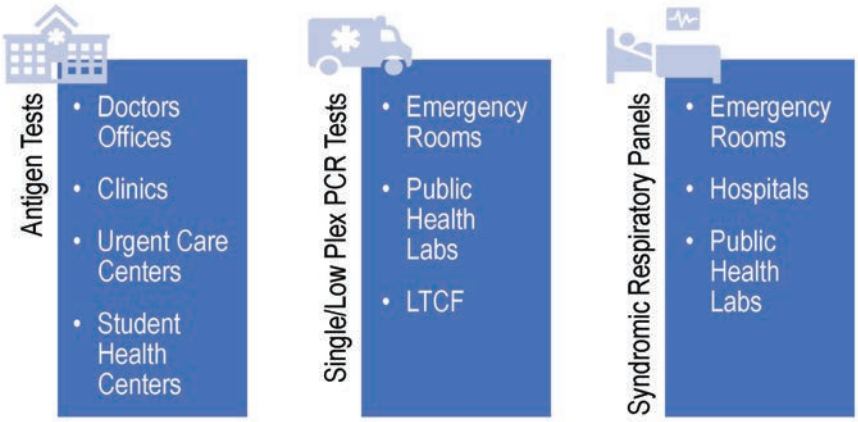

Figure2. Schematic of Potential Uses for Testing of Respiratory Pathogens

The CDC also commented that infection with SARS-CoV-2 and other pathogens has been reported and that detection of one pathogen does not indicate there is not an infection with SARS-CoV-2 as well.[14] Rapid identification of these pathogens can help providers administer proper antiviral and/or antibacterial therapy in an actionable timeframe, or avoid giving an antibiotic or antiviral altogether, which can aid in the fight against AMR. Even if therapy has been started, some studies have said that stopping unnecessary therapy early may be linked to shrinking drug resistance.[15] These panels can also play a critical role in infection control and hospital admissions.

Larger diagnostic panels can aid in determining the cause of respiratory infection in many ways. For instance, a rapid result for a normally healthy person may allow for decreased hospital admissions, as seen in a recent publication where 8.4 percent of adults were not admitted to the hospital because of the rapid diagnostic test result, which ultimately saved the hospital time and made beds available for sicker patients.[16] Earlier results from a rapid multiplex panel can allow hospitals to focus on patients that need to be admitted and potentially segregated to a designated COVID-19 ward/area or triaged to another area due to other known respiratory illnesses. This will be crucial to help ensure that patients – especially those undergoing surgeries, in recovery, and with underlying comorbidities – are not exposed to SARS-CoV-2 or any of the other respiratory pathogens discussed here. Likewise, hospital patients being discharged to rehabilitation or long term care facilities who have a negative SARS-CoV-2 test result and have respiratory symptoms may need to be assessed other respiratory illnesses.

Matching the test to the care setting

Now that options for SARS-CoV-2 and influenza diagnosis are more accessible through avenues such as antigen testing, it will be important to determine which type of test is needed for different patient groups (See **Figure 2**). It remains to be seen how antigen-based tests will play a role during the upcoming respiratory season and where they best fit into the clinical care pathway. In the past, antigen testing for influenza has not been deemed the gold standard due to the low sensitivity and specificity for these tests, driving conversion in many laboratories to molecular-based methods.[17] Additionally, these viral antigen-based tests cannot rule out infection with other agents, an important consideration for certain populations, such as those with any comorbidities. During the upcoming respiratory season, as the scientific and medical community prepares to line the battlefield for an uncertain future, there is a definite need to ensure they are armed with the right test, at the right time, to provide the clearest clinical picture, especially for patients at a higher risk of clinical complications.

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[1] Zhou, Fei, et. al. (2020) Lancet; 395:1054-62.

Point-of-care-testing takes center stage to meet demand for COVID-19 diagnostics

By Kim Futrell, MT (ASCP), MSHI

Many experts say that a global pandemic was inevitable. Amid cuts in funding, public health laboratories do their best to be prepared to manage unpredictable global emergencies. But in spite of these efforts, management of the novel SARS-CoV-2 has been less than ideal, and the virus continues to raise challenges and create questions.

Laboratories of all types have had to be nimble and adapt "on the fly" in order to manage the changes in testing volumes; both the drop in non-urgent testing, and the pressing demand for more COVID-19 testing. Point-of-Care Testing (POCT) is being touted as a crucial part of an integrated solution, and laboratory professionals are needed to ensure those tests are performed properly and results are interpreted with knowledge about the testing limitations.

Off to a rocky start

Right out of the gate, there were struggles with COVID-19 laboratory testing. From the beginning, testing was roadblocked by contamination issues with a RT-PCR test from the Centers for Disease Control and Prevention (CDC). Early bungling of testing efforts gave the virus time to infect thousands of people and limited testing exacerbated distancing and quarantine efforts.

Once laboratories had permission to develop tests and the U.S. Food and Drug Administration (FDA) relaxed regulations for commercial assay developers, testing options began to explode with varying degrees of efficacy. From there, laboratories faced shortages of reagents, collection swabs, and personal protective equipment (PPE).

While laboratories faced an initial drop in testing volumes for routine testing, they simultaneously faced the dire need for rapid COVID-19 testing. Many laboratories are still struggling to ramp up testing and speed turnaround times to help diminish the spread of COVID-19.

Several factors continue to increase the demand for testing, such as:

- increasing spread of the virus
- testing for preoperative patients
- testing in federally qualified health centers, nursing homes, and prisons
- orders from drive-through community events
- organizations bringing employees back to work
- universities bringing students and faculty back to campuses

Slow turnaround times delay contact tracing

Supply chain bottlenecks and staffing limitations have resulted in long turnaround times (TATs) at a time when rapid results are imperative to perform contact tracing and slow disease progression. Test results for the novel coronavirus often take so long that the results are useless in efforts to control the disease. An additional concern is that slow TATs discourage people from getting tested and practicing social distancing.

Some testing sites are struggling to provide results in five to seven days. Others are taking even longer. Long TATs are making it impossible for the United States to replicate the strategy used by other countries to effectively contain the virus – test, trace, and isolate.[1] Delays in testing mean public healthcare workers are not able to notify the contacts of people who test positive. As a result, people continue to spread the virus without knowing they are infected. Anthony Fauci, MD, Director of the National Institute of Allergy and Infectious Diseases (NIAID), explained in a July podcast interview with *The Wall Street Journal*, "If you're going to do contact tracing and the test comes back in five to seven days, you might as well not do contact tracing because it's already too late."[2]

According to a study performed at Harvard University, 4.3 million people need to be tested daily to gain control of the U.S. outbreak and begin to get back to normal. As of June, only 16 states had reached this mitigation benchmark, and of those, only four were doing enough testing to suppress the virus.[3]

Overcoming barriers and addressing challenges

As always, top laboratories find ways to address patient and public health needs, overcoming barriers to the best of their ability. Many laboratories have opted for an integrated approach, adopting multiple testing platforms to alleviate supply shortages and keep up with testing volumes. With a combination of different platforms and vendors, laboratories can ramp up testing capacity and help address supply chain issues. For example, laboratories in Alaska have managed to overcome COVID-19 testing obstacles, resulting in Alaska having the lowest number of COVID-19 deaths per capita in the United States.

A local manufacturer has been selected to deploy 3D-printed collection swabs to address the shortage, and testing is being performed in Alaska's own public health laboratories. In addition, they have embraced the rapid TAT of POCT, are distributing these devices, and training operators in order to mitigate disease spread.[4] Without a centralized federal testing plan, Alaskan officials put together an effective testing program that helped track the outbreak. Their prompt action and focus on the distribution of testing devices and end-operator training allowed them to stand up testing and tracing before the virus could rapidly spread.

Rapid POCT in the spotlight

The need to quickly act to lessen the virus' deadly impact is making fast TAT the number one priority in COVID-19 testing. When speed of results is vital, such as in a worldwide pandemic, POCT becomes imperative. Even a less-sensitive result is significantly better than taking forehead temperatures in a doorway as people enter a building.

There are now numerous POCT options available for COVID-19 testing, including PCR, as well as antigen and serological tests (see Figure 1). Both molecular and antigen tests can be used for diagnostic purposes. Molecular tests use nucleic

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Types of SARS-CoV-2 Assays			
1	Molecular	diagnose active infection	Reverse transcription polymerase chain reaction (RT-PCR)
2	Antigen*	diagnose active infection	Lateral flow, others; *Negative results should be confirmed with molecular test
3	Serological (Antibody)	exposure history/immune status	Lateral flow, ELISA, Chemiluminescent immunoassay, others
• Each category has different: clinical utility, specimen types,characteristics, and limitations • All are available as a POCT			

acid amplification technology to detect viral nucleic acids in SARS-CoV-2's RNA. Molecular testing typically has the highest sensitivity and specificity. Antigen tests detect nucleocapsid antigens that are present in the respiratory system during an active infection. Antigen tests typically have high specificity but lower sensitivity in comparison to molecular tests, lending to a greater number of false negative results.

Antibody testing is not yet widespread, and researchers do not know if the presence of antibodies infers immunity. Going forward, widespread use of antibody tests could help determine how much of the population has had the virus, but the tests cannot detect cases in the early stages of disease. For each of these testing methodologies, results must be interpreted alongside patient clinical information and symptoms.

The rapid introduction of so many tests to the market, the need for proper collection techniques, and concerns about lower sensitivity and specificity set the stage for laboratory professionals to ensure testing is performed appropriately. Herein lies an opportunity for laboratory professionals to explain the proper use of POCT and ensure that samples are being collected and results are being interpreted correctly. While the lesser sensitivity and specificity of POCT is acknowledged as an issue, its rapid TAT is a worthwhile trade-off in patient scenarios where speed is of the essence.

POCT for vulnerable populations

Elderly patients residing in skilled nursing facilities and nursing homes are a particularly vulnerable population. To help mitigate disease spread in this group, the Department of Health and Human Services (HHS) has begun distributing FDA-authorized POCT diagnostic devices to nursing homes in COVID-19 hotspot areas to facilitate on-site testing for patients and staff. This effort is intended to augment their current capacity for testing and improve their ability to quickly respond and prevent disease spread.

"Access to rapid point-of-care testing in nursing homes will further protect our Nation's most vulnerable patients," said ADM Brett P. Giroir, MD., Assistant Secretary for Health at the Department of Health and Human Services (HHS), in a press release.[5]

Also, to protect vulnerable populations, HHS has awarded $760 million to purchase the Abbott BinaxNOW COVID-19 Ag Card, which costs approximately five dollars per test and provides results in about 15 minutes. The test includes a smartphone app that allows patients to receive their test results.[6]

The laboratory's evolving role

The rapid spread of COVID-19 across the world has exposed major gaps in the abilities of most countries to respond to a virulent new pathogen. Rapid, reliable testing is crucial to understanding the spread of the pandemic and to mounting an appropriate response. Moving forward, as we work to control the pandemic and plan for the future, a key lesson is that early availability of diagnostic testing is of great value for patient management and public health. Thus, the development, validation, scale-up in manufacturing, and distribution of diagnostic tests must be a key priority in early preparation during an emerging infectious disease outbreak.

Rapid, integrated laboratory testing that enables quick contact tracing and immediate quarantine is part of the solution to help quickly reduce the spread of the COVID-19 virus. POCT is recognized as a key component to address the TAT challenges and facilitate effective contact tracing. While POCT is imperfect, when performed as intended, its rapid TAT is a worthwhile trade-off in certain patient care situations.

However, the complexities and limitations of POCT require knowledgeable and diligent oversight by the laboratory to ensure reliable results. Laboratory professionals who have training and knowledge about testing methodologies and limitations are well-suited to help determine when and where POCT is appropriate and to help ensure that collection and testing is being performed accurately. Medical laboratory scientists should embrace POCT as a powerful tool in the right places when speed is critical and utilize their knowledge of POCT as an opportunity to showcase their contribution to the healthcare team.

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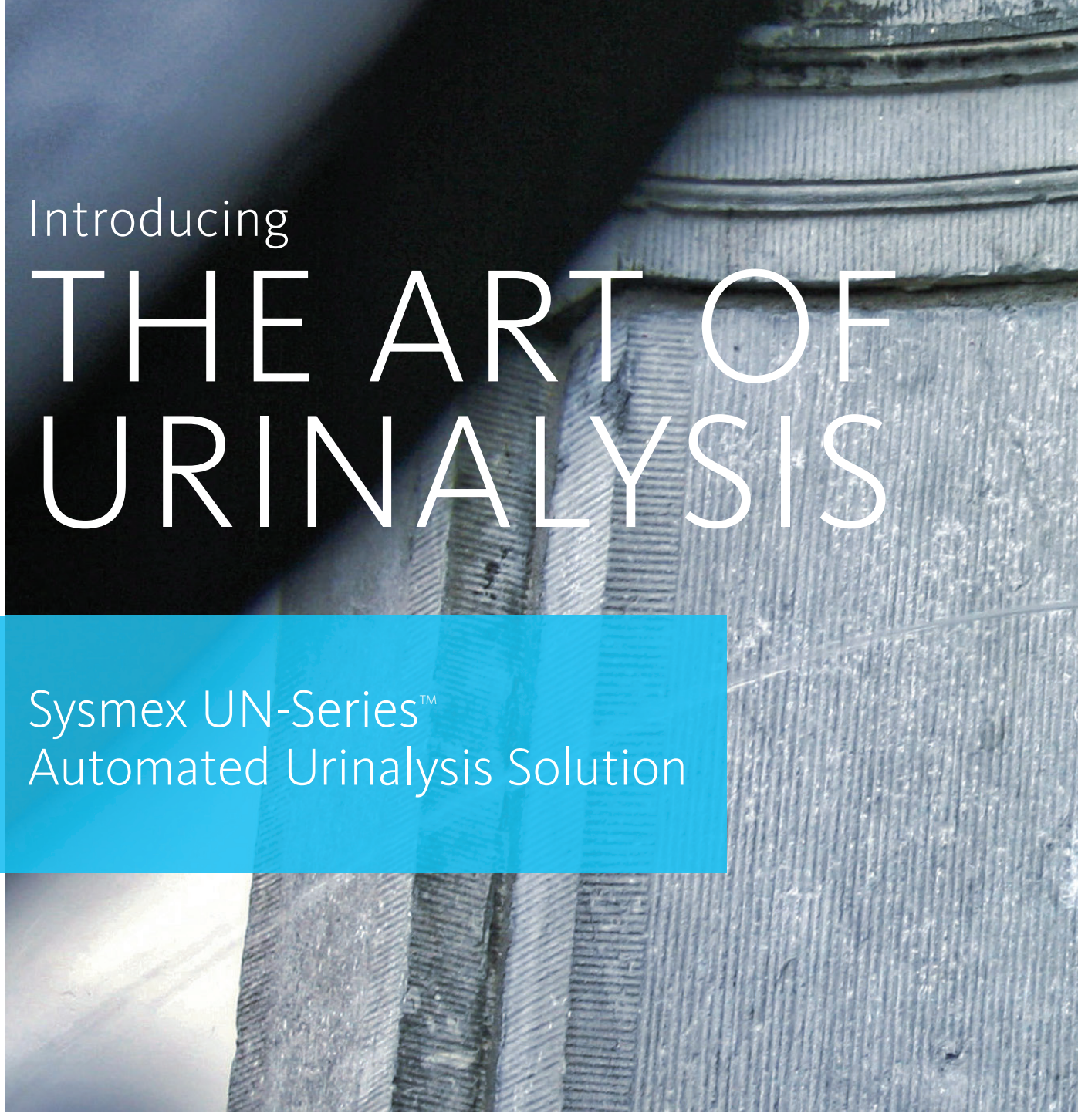

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The recent MLO survey illustrates how labs are coping with SARS-CoV-2 testing and procedures

The impact of COVID-19 on Molecular Diagnostics

By Brenda Silva

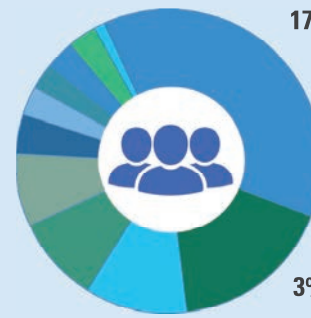
When gathering data on infectious diseases that demonstrate the potential to become a worldwide threat, the molecular diagnostics industry faces various challenges.

As more suspected cases are reported, increased testing demands seek to confirm infections and guide the best practices to treat patients and their symptoms. Because of this year's global severity of the SARS-CoV-2 virus and its resulting COVID-19 disease, clinical labs were presented with a new challenge – performing tests that began with numbers in the hundreds which have now reached into the millions.

In our fourth and final "State of the Industry" survey topic for 2020, *Medical Laboratory Observer (MLO)* focused how labs are dealing with increased testing demands, the types of tests chosen and/or preferred by clinical labs, and how the emergence of the SARS-CoV-2 virus and the subsequent COVID-19 disease impacts daily lab procedures.

Almost half of the survey respondents are in supervisory positions, such as lab managers, administrators and supervisors, working in hospital labs and healthcare systems. With survey respondents holding positions in all areas of the clinical lab industry and with all levels of industry expertise, we received a wide range of opinions and experiences in the replies.

RESPONDENT TITLES



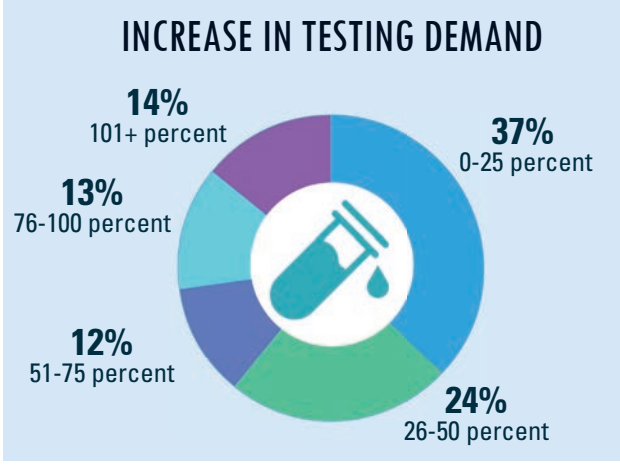
- **38%** Lab Manager, Administrator, Supervisor
- **17%** MLS-Medical Laboratory Scientist
- **11%** Lab Director
- **9%** Section Manager, Dept Head
- **8%** Chief, Asst Chief, Medical Technologist
- **4%** Consultant
- **3%** Compliance, QA Coordinator, Manager
- **3%** Microbiologist
- **3%** Pathologist, Physician
- **3%** POCC, POCT Coordinator
- **1%** Clinical Chemist

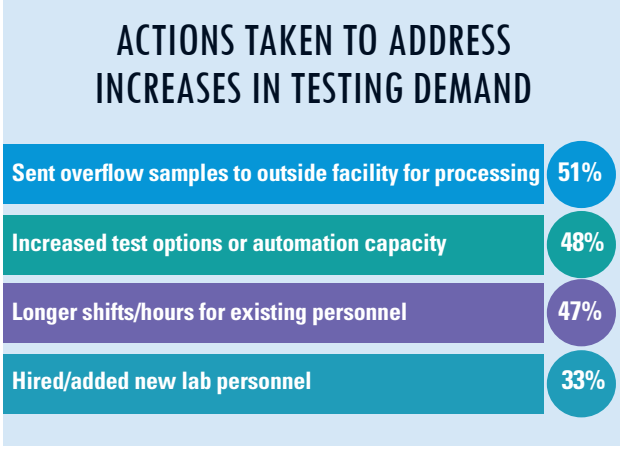
RESPONDENT FACILITIES

- **88%** Hospital lab/Health System Lab
- **10%** Commercial Lab
- **1%** Academic/Research Lab
- **1%** Specialty Lab (i.e. blood banking facility)
- **1%** Other

INCREASED LAB TESTING DEMANDS

With the emergence of the SARS-CoV-2 virus, already-increased lab testing demands grew even more in an attempt to keep pace with suspected cases of COVID-19. When asked to what degree testing demands have increased, over one-third of respondents indicated that demands at their facilities have grown up to 25 percent. Accounting for labs where demands have grown 26-50 percent were one-quarter of respondents.





As lab testing demands have increased and continue to grow at a staggering rate, we asked how labs are addressing these new demands. The most common answer was to send the overflow samples to an outside facility for processing – the choice of approximately half of survey respondents. Following as a close second choice was to increase test options or automation capacity for higher throughput. Additional replies indicated that some labs chose to address the problem in-house as much as possible with longer shifts/hours for existing personnel and/or hire/add new lab personnel.

Because the testing demands have grown at exponential rates for some labs, some concerns have also emerged about the level of confidence laboratorians have in the accuracy of COVID-19 tests.

Leonard Scinto, MS, MPA, DLM(ASCP), Director of Laboratory Services at North Shore Medical Center in Miami, FL, asserted, "Many laboratories not having any molecular testing experience have been thrust into a situation that forced them to make decisions with very limited knowledge in a short time frame."

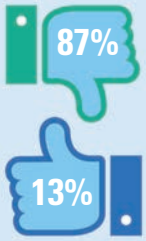
In agreement with Scinto is Linda Minnich, SM(NRM-ASCP), MS, Operations Manager Virology at Charleston Area Medical Center (CAMC), located in Charleston, WV. She summed up the issue of test confidence by saying, "Some are good and perform as claimed. Others have had issues that became obvious as they were utilized more. The limited testing for the FDA EUA has required more evaluation by the users at a time when they needed to get moving."

LAB SUPPLIES AND SHORTAGES

Keeping pace with the increase in lab testing has created much higher demands for personal protection equipment (PPE) to help safeguard lab personnel and healthcare workers against the risk of infection. In addition, test supplies – including disposable products such as PPE (masks, gloves, face shields, etc.) and consumables such as swabs, controls/reagents, and transport media – had many labs reporting difficulty in supply chain acquisition of these products.

The overwhelming majority of survey respondents indicated they did have, and possible still do have, difficulty in maintaining a supply of testing products to meet their increased lab testing demands. On the other hand, a small percentage of replies indicated they have adequate testing supplies to meet the daily demands placed upon their lab personnel.

ABILITY TO MAINTAIN TEST SUPPLIES



NO, a lack of sample-related products has impeded our testing capacity at times

YES, have adequate testing supplies to meet the increased testing demands

TEST SUPPLIES MOST AFFECTED

76% Testing Kits
74% Swabs/Consumables
66% Transport Media
44% PPE
32% Controls/Reagents

However, not all items currently in need are items that can be easily ordered from a manufacturer or supplier. Lately, labs have found that the things that would matter the most during the current pandemic are things that are the hardest to come by.

Scinto said, "I wish we had more time. More time to train our laboratory staff and educate our clinicians on the testing methods and their limitations. More time to develop effective supply chain strategies to minimize disruptions in testing. More time to recognize the many hours our laboratory personnel worked to provide continuous laboratory information to help manage patient care."

Minnich added, "CAMC has a great virology staff who have really stepped up to the plate for patient care. We have an M2000 and Panther, but reagents and supplies have been the issue. This week, no tips or deep wells, next week it is reagents. It has been very challenging to keep up with what we have, what is ordered and what is not coming."

TEST PREFERENCES AND INFLUENCES

When asked about lab preference for molecular diagnostics tests being used in COVID-19 lab testing, reverse transcriptase quantitative polymerase chain reaction (rRT-qPCR) was clearly the most popular reply, followed by rapid antigen tests. In further inquiries, *MLO* wanted to know the main reason these were the top two answers for the majority of responses.

TYPES OF MDx TESTS USED FOR COVID-19

70% Reverse Transcriptase Quantitative Polymerase Chain Reaction (rRT-qPCR)
37% Rapid Antigen Test
8% Reverse Transcription Loop-mediated Isothermal Amplification (RT-LAMP)
6% Recombinase Polymerase Amplification (RPA)
1% CRISPR-based diagnostics

Answers indicated that availability was the most-common reason, which very likely had heads nodding in agreement due to the immediate need for testing supplies in suspected cases of COVID-19. Following availability, choices were seemingly dictated by factors other than having a test immediately ready for use. Many replies concerned the accuracy and/or reliability of results, which can serve to eliminate retests due to questionable results. A range of other choices indicated turnaround time and test cost as factors for test preferences, suggesting the urgency of test results and the influence of department or facility budgets as primary concerns for test choices.

Additional factors that could play an important role in the choice of lab tests and equipment in the future, according to Nikos Pavlidis, VP/GM of Molecular Diagnostics for BD, located in Sparks, MD, include a nod to automation among other considerations.

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References: 1. Knabl L et al. Comparison of the BD MAX Enteric Bacterial Panel assay with conventional diagnostic procedures in diarrheal stool samples. *Eur J Clin Microbiol Infect Dis.* 2016;35(1):131-136; **2.** Hirvonen JJ et al. Comparison of BD Max Cdiff and GenomEra C. difficile molecular assays for detection of toxigenic Clostridium difficile from stools in conventional sample containers and in FecalSwabs. *Eur J Clin Microbiol Infect Dis.* 2015;34(5):1005-1009; **3.** Bauman M. Transitioning from culture to molecular: implementation and integration of BD MAX™ Enteric Bacterial Panel at Cincinnati Children's Hospital. BD Advertorial. Franklin Lakes, NJ: Becton, Dickinson and Company; 2015; **4.** Le Blanc L et al. Cost-effectiveness and laboratory workload efficiency of 8 C. difficile testing algorithms. Poster presented at: American Society for Microbiology; May 30–June 2, 2015; New Orleans, LA; **5.** Centers for Disease Control and Prevention. Recommendations for the laboratory-based detection of Chlamydia trachomatis and Neisseria gonorrhoeae—2014. *MMWR Recomm Rep.* 2014;63(RR-02):1-19; **6.** Powell S et al. The impact of molecular approaches to infectious disease diagnostics. *Medical Laboratory Observer* website. http://www.mlo-online.com/the-impact-of-molecular-approaches-to-infectious-disease-diagnostics.php. Updated August 2, 2015. Accessed May 15, 2017.

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"The key points here are that your categories of accuracy, speed to result, and costs all are relevant factors, but we would add automation/ease of use/ workflow simplicity and open vs. closed systems, which may be additional categories to consider for the future."

When considering reasons to use one test over another, J. Kent Morgan, PhD, Chief Science Officer at Veo Diagnostics, located in Loveland, OH, asserted, "It is important to consider the value of information that results from each test type. For instance, molecular tests can only provide an answer to the question of whether or not an individual was at the moment of sampling infected with the SARS-CoV-2 virus. This effectively limits the value of molecular testing to 'currently sick' people to either validate or rule out an individual as having COVID-19."

Morgan continued, "Conversely, antibody tests can be used to help show whether a person or group of individuals has a current or past immune response to the SARS-CoV-2 virus. Antibody tests can be used to screen for immune response and possible disease prevalence in both individuals and larger populations. Antibody test results could be valuable to help understand and make informed decisions related to disease management for an individual or a larger community of people."

QUESTIONABLE RESULTS AND PROCEDURES

Increased lab testing demands have simultaneously increased the potential for questionable test results, attributable to both manual and automated handling procedures. When questionable results occur, many labs tend toward what is probably the fastest and easiest option for reverification of results – repeating the test with a different test/employee – evidenced as the top solution, according to more than half of survey respondents.

However, should retesting not produce the desired results, many laboratorians are then likely to send the questionable results to another lab for verification and/or a second test. If the same questionable results occur a second time at a secondary lab, some labs opt to begin the process all over again by verifying that the procedure followed was correct from the beginning of the process. These same labs may also look to collect another specimen, conduct a serology test, and repeat the test with the same sample to see if the results are the same as the first test.

When asked what steps – if any – labs are taking to reduce the number of potential false positive test results, nearly one-third of replies suggested that lab personnel repeat the test with another method and compare the results, while an equal third asserted that laboratorians verify all pre-analysis steps to ensure they are performed correctly.

HANDLING QUESTIONABLE MOLECULAR TEST RESULTS

- 57% Repeat the test with different employee | equipment | test
- 26% Send results to another lab for verification and second test
- 7% Verify procedure followed was correct
- 4% Check for analyzer operational issues

STEPS TAKEN TO REDUCE THE NUMBER OF FALSE POSITIVE TEST RESULTS

- 29% Repeat the test with another method and compare results
- 29% Verify all pre-analysis steps are performed correctly
- 21% None
- 16% Repeat the test with the same sample and new extractions

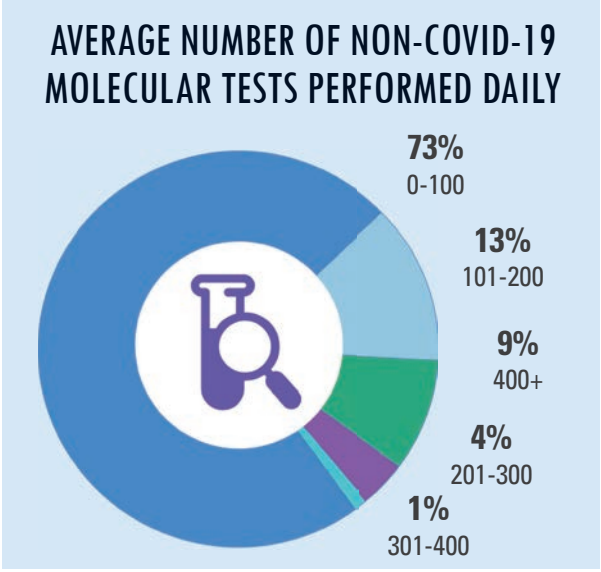
Perhaps the most surprising of all is that among survey respondents, a fair amount admitted they are doing nothing to prevent or reduce potential false positive test results, which calls into question the issue of test result accuracy and reliability.

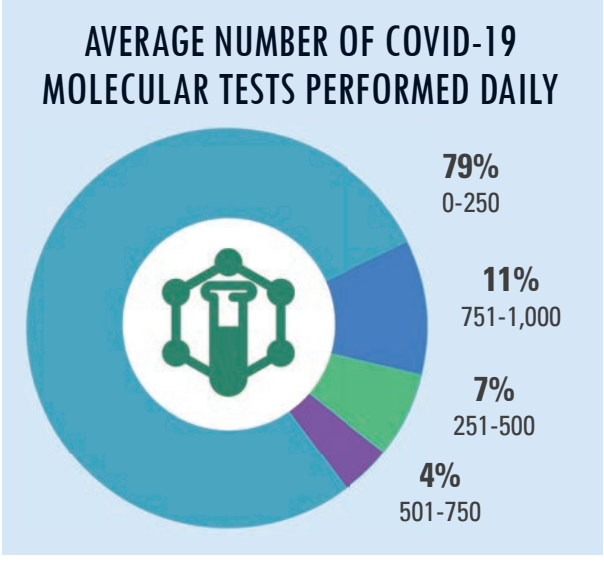
Scinto points out, "Previously, we relied on FDA 510(k) approved assays, which underwent several years of manufacturer performance validation. Now, laboratories are making testing decisions with SARS-CoV-2 assays that underwent several weeks of validation with FDA EUA (emergency use authorization) approval. A fair number of assays have since undergone FDA clarification and revisions due to analytical and performance issues that arose in the field. A diminished level confidence in the assays and the manufacturer was the outcome. To circumvent this, many laboratories opted to create LDT assays and apply for EUA certification. Thus, allowing them to internally validate and understand firsthand the performance characteristics of the assay and the test results they are reporting."

ALL IN A DAY'S TESTING

Looking to COVID-19 hot spots, some cities that previously had very low numbers of confirmed cases can experience a spike in cases and vice versa for cities that were hot spots at one time, but which are now seemingly less dominant locations for the disease. As such, the demands for COVID-19 tests vary from day to day, depending on various scenarios that allow an outbreak of infection to occur.

With this in mind, the MLO survey looked to find an average number of non-COVID-19 molecular-based tests that are performed on a daily basis by labs. The answer chosen most often was 100 or fewer tests, chosen by the greater majority of respondents. A similar survey question asked respondents to indicate the average number of only COVID-19-related molecular-based tests performed daily in labs. For this question, the top answer was 250 or fewer tests, also reported by approximately three-fourths of survey respondents.





NEW REGULATIONS FOR TEST REPORTING

In an effort to alleviate concerns about public health, new regulations require reporting of all COVID-19 test results. As such, there are four primary agencies that are responsible for receiving the required reports from labs, including state health departments, local health departments, the Centers for Disease Control and Prevention (CDC), and the Federal Emergency Management Agency (FEMA).

AGENCIES WHERE LABS REPORT THEIR RESULTS

87% State Health Department
36% Local Health Department
12% CDC
10% FEMA

In addition, a small group of additional agencies have also been assigned to collect COVID-19 test data as well, including central labs, assigned county agencies, the U.S. Department of Health and Human Services (HHS), The Joint Commission, assigned universities, and the U.S. Department of Veteran's Affairs.

HOW LABS REPORT THEIR RESULTS

50% Use specified software for results reporting

23% Aggregate test results, only data requested

14% Digital report of data results, including any inconsistencies/issues

13% Aggregate test results, all data

To make reporting test results easier, many labs/lab managers are taking advantage of reporting options made available to them. Half of survey respondents indicated using specified software for results reporting, while others aggregate test results and send the data collected or requested of them.

LOOKING TO THE FUTURE

While not included as a question on the available MLO survey, our editorial staff followed the survey by reaching out to clinical diagnostics companies to find out what areas or issues within molecular diagnostics they felt needed more attention going forward in the future.

According to Michelle Bosch, Senior Director, Global Commercial Marketing, Diagnostics, at Meridian Bioscience, located in Cincinnati, OH, "There is a critical need to deliver quality diagnostic solutions that are flexible and scalable, as healthcare systems continue preparing for increased testing capacity during this unprecedented time. Supply chain optimization must be a priority to continue delivering all essential diagnostic products to support our healthcare systems in providing the necessary care and treatment to patients."

Adding to Bosch's comment, Morgan from Veo Diagnostics said, "Test accuracy should be an area of focus for Molecular Diagnostics and the primary concern of any diagnostic lab environment. The result of accurate testing has shown to produce more reliable data, which can help communities make smarter decisions on structuring their environment."

Pointing out an unknown but potentially serious impending issue, Michelle Tabb, PhD, Chief Scientific Officer at DiaSorin Molecular, located in Cypress, CA, said:

"Perhaps the most important area to keep in mind is the impact flu may have on the upcoming respiratory season while COVID-19 is still present. With similar symptoms and different treatment options, it will be critical for labs to ensure they can detect and differentiate between SARS-CoV-2, Flu A, Flu B and potentially RSV, so that patients get the correct diagnosis and treatment."

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Potential impacts of EU IVD-Regulation on the clinical flow cytometry lab

By Maurizio Suppo, PhD

Like many other ideas that are intended to improve existing products or procedures, the new European IVD Regulation (IVD-R) 2017/746 road is paved with good intentions. However, some of these intentions may potentially render the daily life of clinical flow cytometry laboratories a lot more complex than what they are now, due to the latest regulations for Laboratory-Developed Tests (LDTs).

Transition period for IVD-R

The legislative text still used to regulate the distribution of all IVDs in Europe is the old IVD Directive 98/79/EC, which was drafted almost 25 years ago and, as with anything old, started to show some severe limitations due to its age – particularly when compared with other IVD legislations in different parts of the world.

A few signs of age of the current IVD-Directive are the fact that companion diagnostic, tumor marker and even the recent COVID-19 (RNA or serological) assays are all in the self-certification class and can be placed on the EU market solely under the exclusive responsibility of their manufacturers without the intervention, supervision and approval of any third party (Notified Bodies).

Aware of the limitations of the existing IVD-Directive, the regulators who wrote the IVD-Regulation (a mix of EU Commission with interventions by the EU Parliament and Council) set the bar very high – in particular for IVDs – and thus, published a new regulation that in terms of complexity and cost, can stand shoulder-to-shoulder with other existing regulatory text and/or content.

In May of 2017, when the EU Commission published the two new legislative texts that will regulate both medical devices (2017/745 MD-R) and IVDs (2017/746 IVD-R) going forward, the transition period that began allowed an IVD manufacturer to place a product on the EU market under the IVD-Regulation; the fact that no one did it up to now maybe due to several reasons among which the most notable are:

- The first couple of IVD-R Notified Bodies (NBs) started to appear only in October 2019 and, up to now, there has been little progress with the name of another one. The UK one should not be counted due to the fact that with Brexit finally happening it will lose its status as of January 1, 2021. In fact, all the focus has been on the nomination of Medical Device-Regulation (MD-R) NBs and then COVID-19 hit the world, and everything stopped. Without NBs, manufacturers cannot have their devices approved as per the IVD-R.
- Launching the first device on the market under the IVD-R implies having all those processes in place for performance evaluation and post-market surveillance, and this is no small task to accomplish.

In its review of the former and new legislative texts, this article will provide a high-level broad coverage of the new EU IVD Regulation and will specifically elaborate on how the EU authorities will regulate the vast majority of the Laboratory-Developed Tests (LDTs), which are currently done in Europe on a daily basis.

IVD-Directive changes to come

Looking to the new year through the lens of the new IVD-Directive, the top four things that will bring about change are:

1. Massive involvement of Notified Bodies on all tests detecting/measuring something.
2. Much higher expectations on how manufacturers demonstrate clinical evidence for their devices.
3. A concept of performance evaluation for the IVD devices, which includes a much reinforced and more sophisticated approach to Post-Market Surveillance.
4. A different approach to Laboratory-Developed Tests (LDTs).

1. Notified Bodies everywhere

All qualitative or quantitative tests fall within the scope of the Notified Body that the manufacturer will have to choose, pay and work with. Considering that around 90 percent of the IVD assays in circulation today do fall in the IVD-Directive self-certification class (no involvement of a Notified Body), this truly represents a revolution for several IVD manufacturers; a paradigm shift.

All those IVD manufacturers that were making assays in the clinical chemistry, endocrinology, allergy, tumor markers and even companion diagnostics will find themselves forced to come to terms with thorough and challenging Notified Body reviewers and will have to convince them that their quality management system is good. This includes that they are properly managing suppliers and, in particular, contract manufacturers, that their design control, performance evaluation and post-market surveillance processes are flawless, and that their assay-specific technical documentation is well structured, complete and has all the I's dotted and the T's crossed.

We start to have the first glimpse of the new audit and TD review fees of the IVD-R NBs and they are very high, as it could be expected considering that we will likely have a third (or a little more) of the number of NBs we have today for the IVD-Directive (much fewer competitors) and an explosion of work (85 percent of IVDs will require NB involvement and approval under the IVD-Regulation vs only 15 percent under the Directive). A major NB (already nominated for the IVD-R) estimated this at a 600 percent increase in workload with respect to the one related to the IVD-Directive.

2. Higher bar on clinical evidence

Manufacturers will have to work harder to prove that their device is worth approval from the NB. In the past (under the Directive framework), NBs were involved only on few IVDs (those listed in Annex II A, B and self-tests) and even for those the NBs were essentially focusing on the analytical performance. Now, under the IVD Regulation, the focus on clinical evidence has broadened the work required, forcing manufacturers to demonstrate also the scientific validity (the link between the

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analyte and the clinical condition) and the clinical performance in addition to the analytical performance. This focus is new for many manufacturers and will imply a lot of work and considerable costs.

3. Performance evaluation at 360º

If you believe that performance evaluation is what you have to do before you launch the product on the market, you have not understood the spirit of the IVD-Regulation.

Performance evaluation is a "cradle to grave" process that must continue well beyond the product launch and has to last until product discontinuation. No performance evaluation plan is complete unless it includes a well thought out and rather elaborate post-market surveillance plan. And such a plan must include the assessment on whether Post-Market Performance Follow-up studies (PMPF) aimed to continuously reassess how the device in question performs when compared with the other similar products. The formal documentation of state-of-the-art or competitor landscape evaluation, another new concept, has become an obligation under the IVD-R.

CE-IVD flow cytometry reagents

The three points above do represent a massive change for IVD manufacturers. A paradigm shift that:

a) Will leave several products on the ground because they will not be "IVD-Rized" due to the cost of filling the gaps and perhaps due to the fact that they have reached the end of their expected life-cycle, and

b) Will probably leave some companies on the ground because they will not be able to rise to the much higher bar imposed by the IVD-R.

These two factors are likely to change the shape of the EU IVD market with possible effects going well beyond the EU.

4. The LDT nuclear bomb

However, there is a fourth element of change that will primarily impact clinical laboratories and not only within the EU. It will also affect IVD manufacturers. And this just by itself is a potential nuclear bomb that, if enforced correctly, will shake-up the world of IVD testing.

The LDT nuclear bomb

Very few people seem to have realized that the regulators who wrote the IVD-R dropped a nuclear bomb on LDTs.

They used the classic "two-punch" boxing technique first by writing Art. 5.1: "*A device may be placed on the market or put into service only if it complies with this Regulation when duly supplied and properly installed, maintained and used in accordance with its intended purpose.*"

Art. 5.1 seems innocuous because it simply states that devices that are placed on the (EU) market have to comply with the Regulation. However, the other punch is delivered with Art. 5.4, which without mentioning them directly, essentially states that all LDTs are considered as placed on the market: "*Devices that are manufactured and used within health institutions (…) shall be considered as having been put into service.*"

The two together (Art. 5.1 + 5.4) equal to the statement: "all LDTs have to comply with the IVD-Regulation."

The spirit of Article 5.5

Art. 5.5 further elaborates on this by providing very few exceptions for LDTs to be outside the scope of the IVD-Regulation. The spirit of Art. 5.5 is that true European Health Institutions (see later definition) shall be allowed to make their own LDTs where there are no commercially available products. This would protect the labs to develop in full freedom LDTs for rare diseases for which no industrial IVD manufacturer bothers to make an assay, or for those emerging diseases (think about the recent COVID-19 situation) for which industry has not yet developed commercially available tests.

However, the limitations imposed by Art. 5.5 are very thorough and they are summarized below:

To develop, manufacture and use an LDT a lab must fulfill all of these requirements:

1. Be a **European** health institution
   a. The IVD-R gives a definition in Art. 2 (29): "*Health Institution means an organization the primary purpose of which is the care or treatment of patients or the promotion of public health.*" Although a definition is given, we still think that it is subject to interpretation and will need to be further clarified. For example, it is not entirely clear whether an EU private lab contracted to do IVD tests on behalf of the national healthcare service can be considered as a health institution or not. For sure, any non-EU lab will not fit the definition and therefore cannot do LDTs on EU citizen samples being shipped to them.
2. Comply with the General Safety and Performance Requirements (GSPR) listed in Annex I of the IVD-R.
   a. This is no small feat. Complying with the GSPR listed in Annex I of the IVD-R is hard work and involves extensive test and documentation.
3. Have an appropriate Quality Management System (QMS)
   a. The European Health Institution lab is required (in order to do its own LDTs) to have a QMS system in place and the IVD-R even goes on to specify that it shall be compliant with the

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ISO-15189 "Medical laboratories — Requirements for quality and competence," which is for a clinical laboratory what ISO 13485 is for an IVD manufacturer. Actually the 15189 is even harder because in addition to the requirement for a QMS that covers all the diagnostic phases (pre-analytical, analytical and post-analytical) it requires the lab to get accredited for each single measurement/analysis they do.

b. The IVD-R also recognizes that there are some countries (France is just one example) where there are national accreditation schemes for clinical laboratories that are equal or even harder than 15189.

4. The EU Health Institution commits not to distribute their own LDT to other legal entities (other laboratories that belong to different hospitals).

5. The EU Health Institution has to justify that the specific (diagnostic) needs of the target population cannot be satisfied by an equivalent test available on the market.

a. The current interpretation of this is that if there is an IVD manufacturer with an IVD-CE-marked assay that fulfills the testing needs of the lab, then such lab cannot do its own LDT and has to buy the IVD-CE-marked assay.

Who will be responsible for the enforcement of these above conditions? For monitoring what clinical laboratories will do? The Health Authorities of the country in which the laboratory is located. Some Health Authorities of a few European countries have already commented that they are fully aware of the enforcement obligations which will be triggered by Art. 5 of the IVD-R and they are actively preparing for it. Others have not commented, so it is not possible to know whether they are preparing for it or not.

Conclusions

The nuclear fallout of Art. 5 described above will reach far. Laboratories that today routinely provide patient-related diagnostic information using LDT technologies (like flow cytometry labs or labs using HPLC and mass spectrometry technology – just to list two examples) will be fully impacted by Art. 5 and its several points.

Few labs of those EU-based Health Institutions will be able to do some LDTs but, practically speaking, only for those rare diagnostic tests which are not in any IVD manufacturer catalog. And even then, the conditions they will have to fulfill will be very heavy.

For the rest of the labs, which represent the vast majority of the clinical labs, it won't be possible to do LDTs in Europe, or they won't be able to do LDTs outside Europe on specimens from European citizens living in Europe which are shipped to them. Stepping up to the requirements of the IVD-R listed in the points above will be, frankly speaking, too difficult for such labs. The only alternative solution is for the IVD-industry to rise to the challenge and transform all these current non-IVD CE-marked technologies into ones fully compliant with the IVD-Regulation.

Maurizio Suppo, PhD, has more than 34 years of experience in the field of regulatory affairs and quality systems in the IVD industry. He held executive positions at Sorin Biomedica (now DiaSorin), Becton Dickinson, Dade Behring and Siemens Healthcare. He has been the Director of the European Diagnostic Manufacturers Association (EDMA) and represented the IVD industry position in the drafting of the European IVD Directive 98/79/EC. ,Suppo joined Qarad in July 2012 and became partner and co-owner in January 2016.

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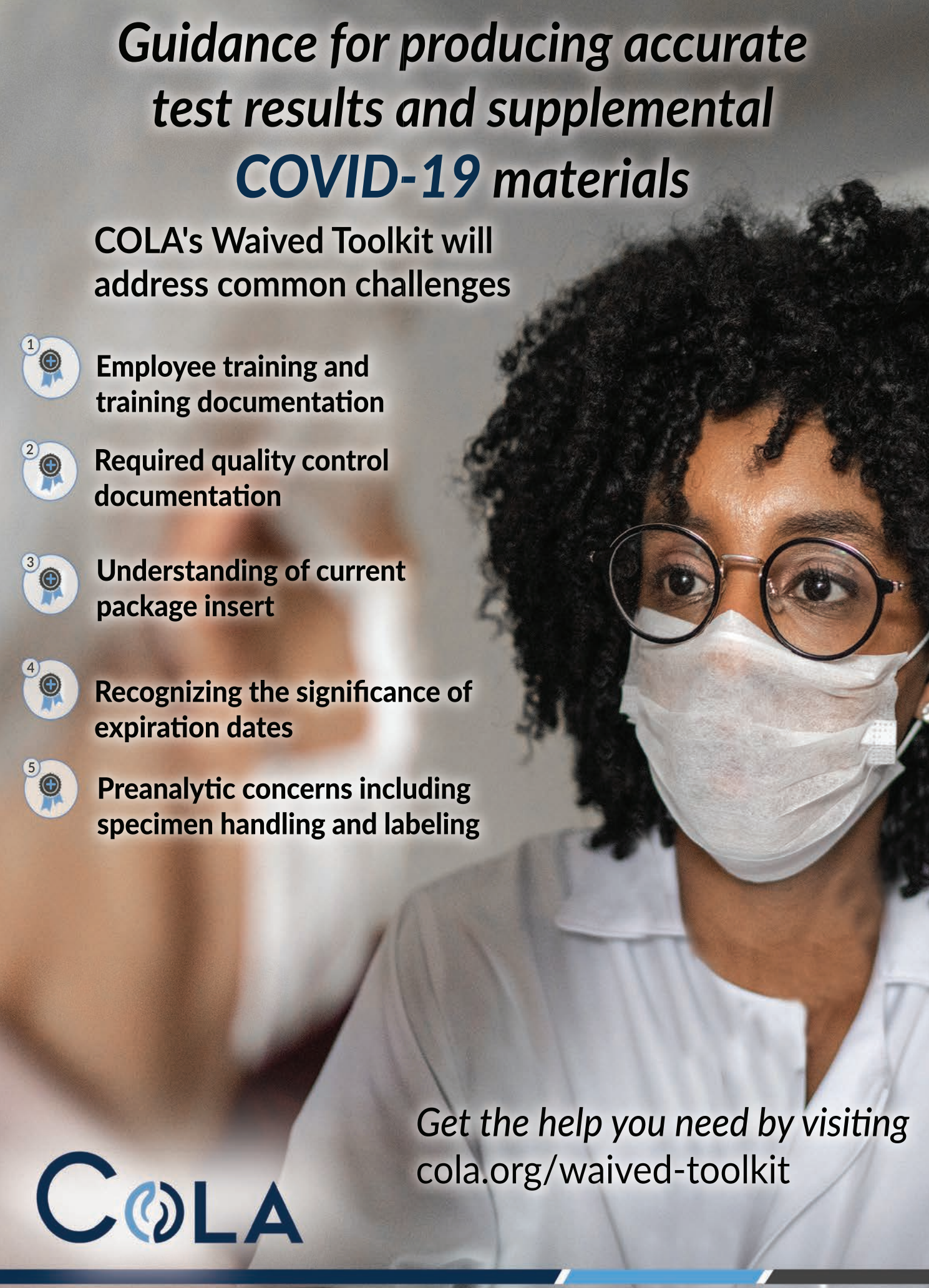

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The reality of virtual laboratory surveys

By Cherri Gregoire, BS, MT (ASCP)

In a world full of "virtual" everything (virtual work environment, virtual tour, and virtual happy hour) it is no surprise that virtual laboratory surveys have become a reality. According to the Cambridge Dictionary, the word "virtual" means "almost a particular thing or quality."[1] It is also no wonder that when a laboratory is selected to participate in a virtual survey, anxiety levels can run higher than usual. We have to ask ourselves the question "how is this going to work?" To answer that question, this article discusses the virtual survey process, which typically includes three phases.

Documentation Review

There is no escaping the fact that documents are going to need to be reviewed – lots of documents. A standard letter sent to a laboratory from an accreditation organization discloses the list of documents to be submitted. Labs can submit their documents in a number of ways: fax, email or by upload. If a laboratory uses a quality management platform to house procedures, quality control data, personnel training and competency records, etc., sharing this information over a connected session with the surveyor is an ideal situation to perform the documentation review portion of the virtual survey.

Some examples of the documents that will be requested: a copy of the CLIA certificate, personnel qualification documents and associated training and competency records, instrument maintenance logs, quality control data and quality assessment reviews. As the documents come in, they are reviewed for acceptability. A surveyor may request additional documentation to ensure the laboratory is maintaining compliance with all standards. Once all of the documents have been submitted and reviewed, the laboratory will proceed to the next stage of the virtual survey process – the scheduled video conference.

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Scheduled Video Conference

The next phase of the virtual survey is the video conference. This is a *scheduled* event that takes place at a date and time mutually agreed upon by the laboratory and the surveyor. The only equipment required is a laptop or tablet computer (preferred) with a camera. Equipment mobility is preferred because the surveyor will want you to "virtually" take them around the laboratory.

There are numerous online meeting platforms that can be used to facilitate the video conference portion of the virtual survey. Microsoft Teams is a good choice, as it does not require that the laboratory download any software in order to meet with the organizer of the meeting.

What kind of opportunities does the video conference afford the lab and the surveyor? First, the surveyor has the ability to speak to any of the laboratory staff. If, for example, the surveyor wants to speak to the laboratory director about delegated responsibilities and then ask the testing personnel to explain how they handle critical results, this can all be easily accomplished.

The camera, too, has many uses. The laboratory personnel can take the surveyor around and let them see testing being performed; the surveyor can take a look inside of a lab's storage refrigerator and check the expiration dates on your reagents (you can actually read them); and the surveyor can check specimen labeling by having personnel hold some specimens up to the camera.

Of no less importance, the video conference provides a lab and a surveyor with a stage for the exchange of information. Questions can be asked and answered, explanations can be provided, and any loose ends from the documentation review portion of the virtual survey can be tied up. This is the laboratory's opportunity to engage with the surveyor in a one-on-one situation.

A survey summation will take place at the end of the video conference. Any citations noted from the documentation review and the video conference will also be confirmed at this time. The lab is then ready to proceed to the final stage of the virtual survey – the brief on-site visit.

On-site visit to confirm lab operations

If the geographical area where the laboratory is located is deemed safe (in respect to whatever it was that created the need to perform surveys virtually), the surveyor will schedule a brief on-site visit with the laboratory within approximately four months of the video conference.

The purpose of the brief on-site visit is to confirm laboratory operations. Laboratories should be prepared to report any significant changes in laboratory operations to the surveyor (e.g. change in laboratory director, change in test menu, and change in annual test volume). The surveyor will perform a walk-through of the laboratory. For all intents and purposes, the survey was complete at the end of the video conference. However, the surveyor can utilize the on-site visit to follow up on any serious or significant issues noted from the documentation review or video conference stages of the virtual survey.

Good candidates for a virtual survey

Not every laboratory is going to be an ideal candidate for a virtual survey. The single most important factor is the size of the laboratory. If a laboratory has an extensive test menu, performs more than 100,000 tests annually, or performs full transfusion services, mass spectrometry or molecular testing, it is not an ideal candidate for virtual survey. The sheer amount of documentation that would need to be submitted for review would be substantial. These types of laboratories are much better

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The evolution of digital decision support in cancer care

By Denise L. Heaney, PhD

As cancer care becomes more sophisticated and more personalized, oncologists and the entire care team face growing time pressure – including the daunting task of sifting through a staggering amount of information. More than a million medical papers are published each year, with nearly 100 clinical trial reports and reviews added every day.[1] In 2018, more than 1,000 new cancer drugs were being studied in clinical trials or awaiting FDA review.[2,3] When patients are facing a potentially life-changing diagnosis, they need confidence that their healthcare providers are considering all the relevant data and making the best possible diagnostic and treatment decisions in a timely fashion.

Taken on their own, vast amounts of health data and information do not automatically add up to improved patient outcomes. Few clinicians have the time to delve deeply into the latest and increasingly complex research and prepare all patient diagnostic information for review with other experts to make a confident decision about the right therapy for each individual patient.

The challenges in harnessing health information today are so complex that no one player can tackle them alone. When companies with complementary expertise in healthcare and technology form partnerships, they can provide clinicians with much-needed clinical decision support tools. By using technology to gather complex information, pull out clinically relevant data and streamline the management of patient information, these tools enable clinicians to make more confident, timely decisions throughout the course of care. In a multidisciplinary tumor board, for example, having a comprehensive view of each patient through a technology-enabled "dashboard" can help specialists use the limited time they have to review all necessary patient data and align on the best possible treatment plan. This process is an important step in delivering more personalized care to patients with a life-threatening disease like cancer.

"It's extremely important to have an accurate diagnosis, which means we need all the information about what is going on with the patient – from all the studies, all the radiology reports, all the lab tests," according to Richard Hammer, MD, Vice-Chair of Clinical Affairs, University of Missouri School of Medicine. "We need to have that all present in one place to make an accurate diagnosis and decide what the best treatment is."

Improving access to essential information

Many new clinical decision support tools employ cloud-based software, which means that participating clinicians on a care team do not have to be in the same room anymore. Instead, they can login remotely to upload, review and discuss patient information from any place, which further supports easier, more informed and timely decision-making by oncology care teams.

One of the critical venues for this collaboration is the tumor board, or a multi-disciplinary team meeting that brings together oncologists, radiologists, surgeons, pathologists, nurse navigators and other specialists that play a key role in cancer care. In under 90 minutes, a typical tumor board needs to review all the clinical perspectives required to fully understand a cancer patient's disease[4] and determine the best possible individual treatment plan. As such, tumor board discussions represent some of the most important minutes in a cancer patient's life.

But running a tumor board is both time- and labor-intensive, and tumor board participants have demanding caseloads. Coordinating meetings, getting all the experts in the same room and organizing patients' medical information – laboratory tests, medical imaging files, medical history, biomarkers, tumor information and more – can be challenging.

"It's extremely important to have an accurate diagnosis, which means we need all the information about what is going on with the patient – from all the studies, all the radiology reports, all the lab tests" -- Richard Hammer, MD.

With cancer care becoming increasingly complex, oncology care teams need a more streamlined approach to clinical workflow and information management. New clinical decision support solutions enable experts from various disciplines in cancer care to upload their patient records in the same dashboard from wherever they are. These digital solutions make virtual tumor boards possible, bringing flexibility to meeting logistics and allowing oncology experts to connect to a broader network for consultation, second opinions and knowledge sharing. Having all of the relevant clinical information available in one place for review by the entire team and not having to switch between systems saves time. It also "facilitates our discussions and leads us to make the best decision regarding therapy for the patient," Hammer said.

Searching databases for actionable insights

Oncology decision support software can also provide automated access to external databases to bring timely and relevant patient-specific actionable insights to treatment decisions. For instance, integrated software applications can pull in the latest National Comprehensive Cancer Network (NCCN) or other clinical practice guidelines for a tumor board discussion, measure and document guideline adherence or variance, and record patient diagnostic and treatment paths. This can also reduce inefficiencies in payer reimbursement and hospital accreditation.

Other available apps can find the latest, sponsor-agnostic clinical trials to help the care team explore patient treatment options. Using patient-specific data, the software can

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targeted for on-site surveys. Applicant laboratories are also not good candidates for virtual survey. It is very important that applicant laboratories get started on the right foot, and an on-site visit is a great way to establish this relationship.

Preparing for a virtual survey

When preparing for a virtual survey, the laboratory should designate a point person for the duration of the virtual survey. This will help with organization and efficient use of time by not having to bring in a new person at each stage of the survey and get them up to speed on the status of the process.

Laboratories should always be in a state of survey readiness. Laboratories should perform a self-assessment of their laboratory and correct any non-compliances prior to the virtual survey.

Laboratories will have 21 days in which to submit the required documentation for the documentation review stage of the virtual survey. It would be wise to prepare for how this will be accomplished. Are you going to fax your documents in? Do you have extra manpower appointed to that task? If your plan is to upload documents, do you have access to a scanner? Perhaps your laboratory can share your documents online with the surveyor via quality management software. If so, you need to make the surveyor aware of this capability and get the logistics of the online meeting worked out beforehand.

Other steps to prepare for the virtual survey involve equipment. In addition, does the laboratory have the necessary equipment for the video conference? Do you have a mobile computer device with a camera? If not, you should arrange to borrow this equipment. Accreditation organizations may allow a lab to borrow this equipment for the virtual survey. Make an effort to schedule the video conference on a date and time when the largest number of laboratory staff will be available. It is important that the laboratory director be available, perhaps the technical consultant, and certainly some testing personnel.

Again, a brief on-site visit will take place approximately four months after the video conference. Treat this visit like a regular on-site survey. This means a lab may want to tidy up the facility and be prepared for a walk-through. Labs also should be sure to report any significant changes in operations to the surveyor.

Value of a virtual survey

Accreditation organizations are collecting data on the virtual process, and time will tell us if the virtual surveys are effective. In the face of a pandemic, performing a virtual survey is better than the alterative, which is to do nothing. Accreditation organizations need to be able to assess laboratory quality and compliance as best we can in these circumstances. At this time, the virtual survey is the best alternative we have to a traditional on-site process.

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Cherri Gregoire, BS, MT (ASCP), is a surveyor for COLA with over 24 years of experience in the clinical laboratory as a generalist, QA coordinator, and technical supervisor. She also has experience in regulatory compliance, POCT, and as a clinical educator for MT student clinical rotations in clinical laboratory science programs.

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automatically search the largest international trial registries to find relevant, local clinical trials with convenient locations and identify home institution options. These programs search in real time, deliver results in seconds, and provide unbiased results to match patients to available trials independent of sponsorship.

Another type of oncology decision support app can search trusted, curated publication databases in real time to discover up-to-date relevant medical literature within seconds. Using embedded instructions, it can automatically query thousands of medical and research publications to receive clinically and therapeutically relevant articles in seconds, expanding the care team's knowledge with current medical literature.

Database query apps can perform these functions without sharing sensitive patient information, which is hosted on a secure cloud infrastructure and encrypted in transmission.

Using data to bring patient confidence

The ability of digital decision support tools to offer remote access, enhanced workflow and automated data management can help oncology teams improve the quality of care, provide more timely answers for patients, and potentially include more patients in tumor boards. Research shows that patients reviewed in a tumor board are more likely to be enrolled in clinical trials, yielding benefits for both current and future patients.[5]

Today's decision support tools can help give patients the certainty that they are getting the best possible diagnosis and the best possible treatment course, and that it all happens in a timely fashion. While the diagnostic and therapeutic decisions are still made by healthcare providers, clinical decision support tools can help them make the decisions in a more accurate, personalized and timely manner.

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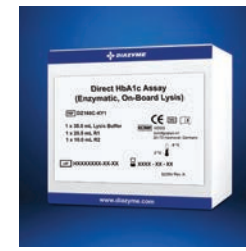

The DZ168C-KY1 (Enzymatic, On-Board Lysis) is NGSP-certified and is used in the quantitative determination of stable HbA1c in venous whole blood samples with on-board blood lysis application. The measurement of HbA1c concentration is for use in monitoring long-term glucose control of persons with diabetes.

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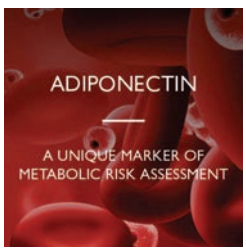

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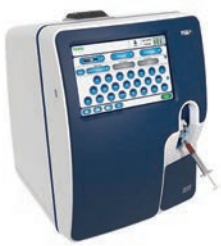

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LABORATORY INNOVATOR

Proficiency testing company successfully makes the grade

By Brenda Silva

Daniel C. Edson, MS, MT(ASCP) is the President of the **American Proficiency Institute (API)**, a company he founded nearly 30 years ago. While in graduate school, Edson invented the world's first blood test for Legionnaires' disease, and years later he established the first virology lab at Lansing's Sparrow Hospital. Currently, more than 20,000 hospital and physician office laboratories subscribe to API proficiency programs.

What has been the biggest change in the types of proficiency testing you provide? What is responsible for any changes in testing? (i.e. Have changes been requested by the industry or were changes demanded of the industry?)

Looking back at the history of API, you can also see the transformations that occurred within the laboratory. API is proud to have been the first proficiency testing provider to offer liquid chemistry samples, complete blood count with automated differential, blood cell photographs, and practitioner-performed microscopy. Almost a decade ago, API revolutionized the field by creating a paperless transmission of proficiency test results directly from a laboratory's information system, and now we offer a one-stop panel of analytic options so that laboratories may monitor their performance. Just this year, API developed one of the world's first proficiency testing programs for SARS-CoV-2, the virus at the root of the coronavirus pandemic. We innovate by anticipating the needs of our laboratory customers.

In what way (if any) has the emergence of SARS-CoV-2 and COVID-19 dictated changes to your proficiency testing so the clinical industry will be better prepared for the next pandemic? What specific kind of COVID-19-related changes (if any) have taken place as part of future-ready training?

We are engaged in a great war with a novel virus, but as laboratorians, we must always be prepared for the next pathogen. We know test results are the cornerstone of contact tracing activities, community-wide sheltering orders, and how disease transmission is controlled. With SARS-CoV-2, it was essential to act quickly and we did. Our SARS-CoV-2 molecular program, introduced earlier this year, contained samples with the whole genome, providing sequence targets compatible with liquid-based molecular assays. A new program was recently introduced that contains sequence targets compatible with swab-based methods. API also offers a SARS-CoV-2 serology proficiency test, as well as a swab-based program for the detection of SARS-CoV-2 nucleocapsid protein, providing exceptional cross platform commutability. I believe it is important to share aggregate data publicly so that we may all learn more in these circumstances. It's why we published results from the first round of API proficiency testing in the *American Journal of Clinical Pathology*.

What do you feel is the greatest challenge of lab proficiency when communicating testing results? What role does proficiency play in today's clinical lab in terms of lab personnel performance and the accuracy of test results?

Laboratories should not have a challenge when communicating their proficiency testing results. It's why we created API DataDirect so that the transmission is seamless and paperless. Proficiency testing is an external, objective measure that assesses the accuracy of clinical laboratory testing. It allows clinical laboratories to review, compare and assess their operation, including staff competencies, equipment and material utility, and specimen handling. It's a vital component of the laboratory's quality assurance.

For lab directors who have limited time and budgets to train new lab hires, what would you recommend as the most important areas to focus on for proficiency testing and certification?

The best advice is to follow the data for your laboratory. Proficiency test results can assist a laboratory director in knowing where and how to make improvements, if warranted.

Looking to the future of the current COVID-19 pandemic, what role can test proficiency play in any future pandemics?

SARS-CoV-2 is a novel coronavirus, meaning it was new and unproven. We are now several months into the COVID-19 pandemic and there is still much we do not know about it. Proficiency testing provides the confidence laboratories crave in these critical times. In the first round of our proficiency testing program for SARS-CoV-2 RNA, the results were rather remarkable. The overall performance, across testing platforms, in the detection challenge was excellent with 97.4 percent correctly detecting the presence of the virus, and 98.3 percent correctly indicating when the virus was not present. This provides needed assurance that laboratories are testing accurately for this novel coronavirus.

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