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MEDICAL LABORATORY OBSERVER

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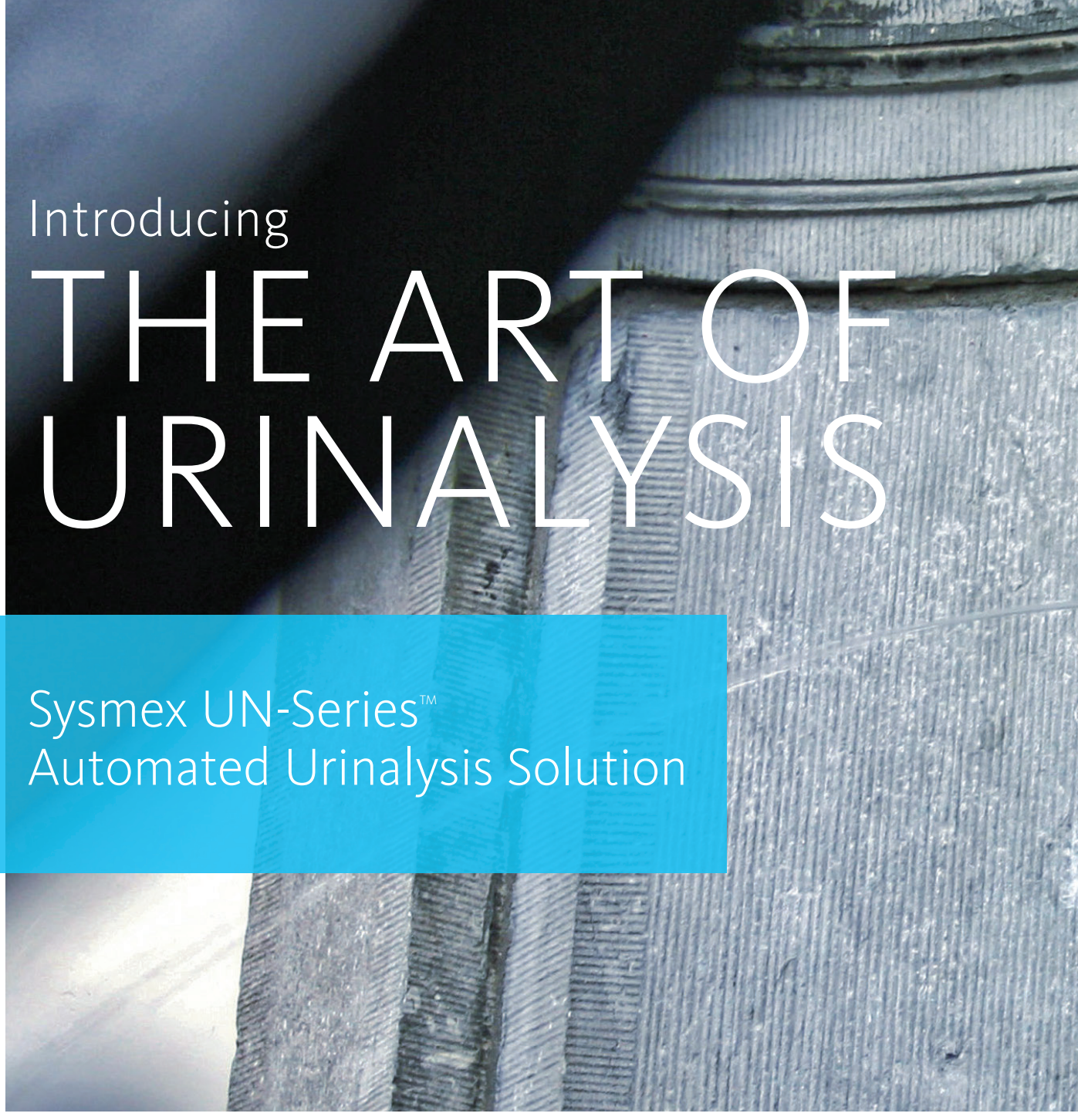

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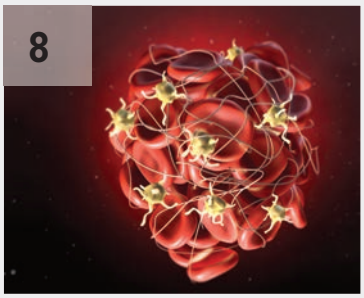

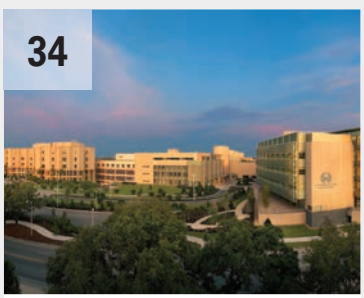

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Research into the long-term impact of COVID-19 is essential

By Linda Wilson
Managing Editor

Emerging evidence suggests that some COVID-19 patients struggle with lingering symptoms – such as fatigue, racing heartbeat and cough – for months. The debilitating virus may also lead to organ damage, increasing the risk for long-term health problems.

SARS-CoV-2 utilizes a spike protein on its surface to bind to angiotensin-converting enzyme II (ACE2) receptors, allowing it to infiltrate cells where it then replicates itself. Because cells lining the lungs, heart, kidney and GI tract express ACE2, scientists suspect that these organs may be vulnerable to damage from SARS-CoV-2.

Studies into the long-term implications of SARS-CoV-2 infections are limited because the disease is still relatively new, but this will likely change as more case histories from patients become available for longitudinal analysis. In fact, it is important for the healthcare field to build knowledge not only about why symptoms linger in some patients but also on the risk of patients developing long-term chronic diseases of the lungs, heart, kidneys or GI tract.

This information will help clinicians understand if there are treatments that might mitigate the risk of future health issues as well as the type of follow-up tests and other care that COVID-19 patients need.

Some sobering research is available already. Here are some examples:

- In a study of nearly 4,000 patients hospitalized with COVID-19, researchers at Mount Sinai Health System said kidney issues, including acute kidney injury (AKI), occurred in 46 percent of hospitalized patients, one-fifth of whom required dialysis. And only 30 percent of patients who were hospitalized with COVID-19 and developed AKI survived and experienced renal recovery.
- Based on a review of more than 100 studies on the impact of the virus on the heart, a researcher at Intermountain Healthcare in Salt Lake City, UT, determined that one out of five patients hospitalized with COVID-19 developed heart issues.
- Writing in the *Journal of the American Medical Association*, Italian researchers found that 87.4 percent of patients reported problems – such as fatigue, joint pain, chest pain and labored breathing – at a mean of 60.3 days after their first COVID-19 symptom.
- French researchers found similar findings in the *Journal of Infection*, reporting that most patients requiring hospitalization for COVID-19 had symptoms for a mean 111 days after returning home. Fatigue and shortness of breath were the most common.

New studies to assess the impact of the disease over the long term are underway, too. For example, the National Heart, Lung, and Blood Institute (NHLBI), part of the National Institutes of Health (NIH), launched an observational study in June in which researchers hope to enroll 3,000 adult COVID-19 patients either while they are hospitalized or after they are discharged. NHLBI researchers will analyze not only chest images but also lab tests for markers of inflammation and coagulation as well as injury to the heart, liver and kidneys.

Clearly, there are holes to plug in the body of research about how SARS-CoV-2 infections impact long-term health and the risk of developing chronic diseases. But based on emerging evidence, laboratorians should be prepared to provide testing services to COVID-19 survivors well into the foreseeable future.

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

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Fast Facts
Spending on diseases

An analysis of 2017 U.S. healthcare spending details the inpatient costs of treating common diseases

$434.2 billion
was the aggregate cost for hospital stays

$38.2 billion
was the total amount spent on treating septicemia – the most spent on any condition treated in hospitals

$14.3 billion
was the total amount spent on treating acute myocardial infarction – the 4th most expensive condition in hospitals

$13.6 billion
was the total amount spent on heart failure – the 5th most expensive condition in hospitals

$9.2 billion
was the total amount spent on respiratory failure – the 7th most expensive condition in hospitals

$7.3 billion
was the total amount spent on diabetes mellitus with complications – the 10th most expensive condition in hospitals

$5.6 billion
was the total amount spent on complications of other surgical or medical care, or injury (initial encounter) – the 15th most expensive condition in hospitals

- **Source:** https://www.hcup-us.ahrq.gov/reports/statbriefs/sb261-Most-Expensive-Hospital-Conditions-2017.jsp

Possible link between COVID-19 and chronic kidney disease

The results of a large-scale study of nearly 4,000 patients led by researchers at the Icahn School of Medicine at Mount Sinai suggest that nephrologists will need to prepare for a significant uptick in patients with chronic kidney disease, the result of exposure to the SARS-CoV-2 virus that causes COVID-19, according to a press release from Mount Sinai.

The study was published in the *Journal of the American Society of Nephrology*.

"We are grappling with a great deal of uncertainty as to how the virus will impact the kidneys in the long haul," says Principal Investigator Girish Nadkarni, MD. "We may be facing an epidemic of post-COVID-19 kidney disease, and that, in turn, could mean much greater numbers of patients who require kidney dialysis and even transplants."

In the study, Nadkarni and a team of Mount Sinai researchers describe consequences of COVID-19 on the kidneys, including acute kidney injury (AKI), which occurred in 46 percent of hospitalized patients, one-fifth of whom required dialysis. Most striking, in-hospital mortality was 50 percent among patients with AKI, versus 8 percent of patients hospitalized with COVID-19 who did not develop AKI. Only 30 percent of patients who were hospitalized with COVID-19 and developed AKI survived and experienced renal recovery.

The researchers conducted a retrospective observational study of 3,993 Mount Sinai Health System patients hospitalized from February 27 to May 30, 2020, reviewing data from electronic health records of patients older than 18 years with laboratory-confirmed COVID-19.

While describing how the Mount Sinai Health System's patient population of racially and ethnically diverse New Yorkers fared during the peak of the pandemic, the authors also show a broader picture of a city unprepared. With New York City being the early epicenter of the COVID-19 pandemic not only in the United States but worldwide, the burden of severe AKI reached full tilt. The authors describe widespread shortages of dialysis nurses, machines, replacement fluids, and cartridges for continuous renal replacement therapy and dialysis.

SARS-CoV-2 infections among healthcare workers may go undetected

A high proportion of SARS-CoV-2 infections among healthcare personnel appear to go undetected, the Centers for Disease Control and Prevention (CDC) noted, based on the results of a study reported in Morbidity and Mortality Weekly Report (MMWR).

To conduct the study, researchers collected blood serum specimens between April 3–June 19, 2020, from frontline healthcare personnel who worked with COVID-19 patients at 13 geographically diverse academic medical centers in the United States, and specimens were tested for antibodies to SARS-CoV-2. Participants were asked about potential symptoms of COVID-19 they experienced since February 1, 2020, previous testing for acute SARS-CoV-2 infection, and their use of personal protective equipment (PPE) in the past week.

Among 3,248 personnel observed, 6 percent had antibody evidence of previous SARS-CoV-2 infection, 29 percent of personnel with SARS-CoV-2 antibodies were asymptomatic in the preceding months, and 69 percent had not previously received a diagnosis of SARS-CoV-2 infection. Seroprevalence by hospital ranged from 0.8 percent to 31.2 percent, with a median of 3.6 percent.

Prevalence of SARS-CoV-2 antibodies was lower among personnel who reported always wearing a face covering (defined in this study as a surgical mask, N95 respirator, or powered air purifying respirator [PAPR]) while caring for patients (6 percent), compared with those who did not (9 percent).

"These findings suggest that some SARS-CoV-2 infections among frontline HCP are undetected and unrecognized, possibly because of the minimally symptomatic or subclinical nature of some infections, underreporting of symptoms, or nonsystematic testing of some personnel with symptomatic infections," the CDC said.

The study was conducted by the Influenza Vaccine Effectiveness in the Critically Ill (IVY) Network, which is a collaboration of academic medical centers in the United States conducting epidemiologic studies on influenza and COVID-19.

The CDC received serum specimens and completed testing for SARS-CoV-2 antibodies with an enzyme-linked immunosorbent assay against the extracellular domain of the SARS-CoV-2 spike protein. This assay uses anti-pan–immunoglobulin (Ig) secondary antibodies that detect any SARS-CoV-2 immunoglobulin isotype, including IgM, IgG, and IgA.

COVID-19 symptoms can persist for months after hospital stay

A research letter published in the *Journal of Infection* showed most patients requiring hospitalization for COVID-19 had symptoms – particularly fatigue and shortness of breath – for a mean of 111 days after returning home, according to a news report on the study from the Center for Infectious Disease Policy and Research (CIDRAP).

Researchers administered a phone questionnaire to 120 COVID-19 patients hospitalized from March 15 to April 14 at the University of Paris-affiliated Beaujon Hospital. Ninety-six patients had been treated in the general ward, while 24 required intensive care unit (ICU) care with artificial ventilation.

The most common persistent symptoms were fatigue (55 percent), shortness of breath (42 percent), memory loss (34 percent), lack of concentration (27 percent), and sleep disorders (31 percent). Twenty-four patients (20 percent) reported hair loss, 20 of whom were women. There was no statistically significant difference in symptoms between ward and ICU patients.

In both groups, slightly more ICU patients reported continued pain on health-related quality-of-life (HRQoL) self-assessment EQ-5D-5L subtests, but there were no other differences. Mean EQ-5D score was 0.86, indicating relatively good QoL.

Mean score on the EQ-VAS was 70.3 percent, indicating good health. "This clearly supports the interest of a full resuscitation for COVID-19 patients despite heaviness of cares," the authors wrote. Thirty-five patients (29 percent) had a Modified Medical Research Council Dyspnea Scale grade of 2 or higher, indicating that they walked slower than their peers because of shortness of breath or had to stop to catch their breath when walking at their own pace.

Researchers show children spread virus that causes COVID-19

In a study of COVID-19 pediatric patients, Massachusetts General Hospital (MGH) and Mass General Hospital for Children (MGHfC) researchers provide data showing that children play a larger role in the community spread of COVID-19 than previously thought, according to a press release from MGH.

In a study of 192 children ages 0-22, 49 children tested positive for SARS-CoV-2, and an additional 18 children had late-onset, COVID-19-related illness. The infected children were shown to have a significantly higher level of virus in their airways than hospitalized adults in ICUs for COVID-19 treatment.

"I was surprised by the high levels of virus we found in children of all ages, especially in the first two days of infection," says Lael Yonker, MD, director of the MGH Cystic Fibrosis Center and lead author of the study, "Pediatric SARS-CoV-2: Clinical Presentation, Infectivity, and Immune Reponses," published in *The Journal of Pediatrics*. "I was not expecting the viral load to be so high. You think of a hospital, and of all of the precautions taken to treat severely ill adults, but the viral loads of these hospitalized patients are significantly lower than a 'healthy child' who is walking around with a high SARS-CoV-2 viral load."

Along with viral load, researchers examined expression of the viral receptor and antibody response in healthy children, children with acute SARS-CoV-2 infection and a smaller number of children with Multisystem Inflammatory Syndrome in Children (MIS-C).

"Kids are not immune from this infection, and their symptoms don't correlate with exposure and infection," says Alessio Fasano, MD, director of the Mucosal Immunology and Biology Research Center at MGH and senior author of the manuscript. "During this COVID-19 pandemic, we have mainly screened symptomatic subjects, so we have reached the erroneous conclusion that the vast majority of people infected are adults. However, our results show that kids are not protected against this virus. We should not discount children as potential spreaders for this virus."

The researchers also challenged the current hypothesis that because children have lower numbers of immune receptors for SARS-CoV-2, this makes them less likely to become infected or seriously ill. Data from the group show that although younger children have lower numbers of the virus receptor than older children and adults, this does not correlate with a decreased viral load. According to the authors, this finding suggests that children can carry a high viral load, meaning they are more contagious, regardless of their susceptibility to developing COVID-19 infection.

NIH establishes Centers for Research in Emerging Infectious Diseases

The National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health (NIH), has announced that it has awarded 11 grants with a total first-year value of approximately $17 million to establish the Centers for Research in Emerging Infectious Diseases (CREID), according to a press release from the NIH. The global network will involve multidisciplinary investigations into how and where viruses and other pathogens emerge from wildlife and spillover to cause disease in people. NIAID intends to provide approximately $82 million over five years to support the network.

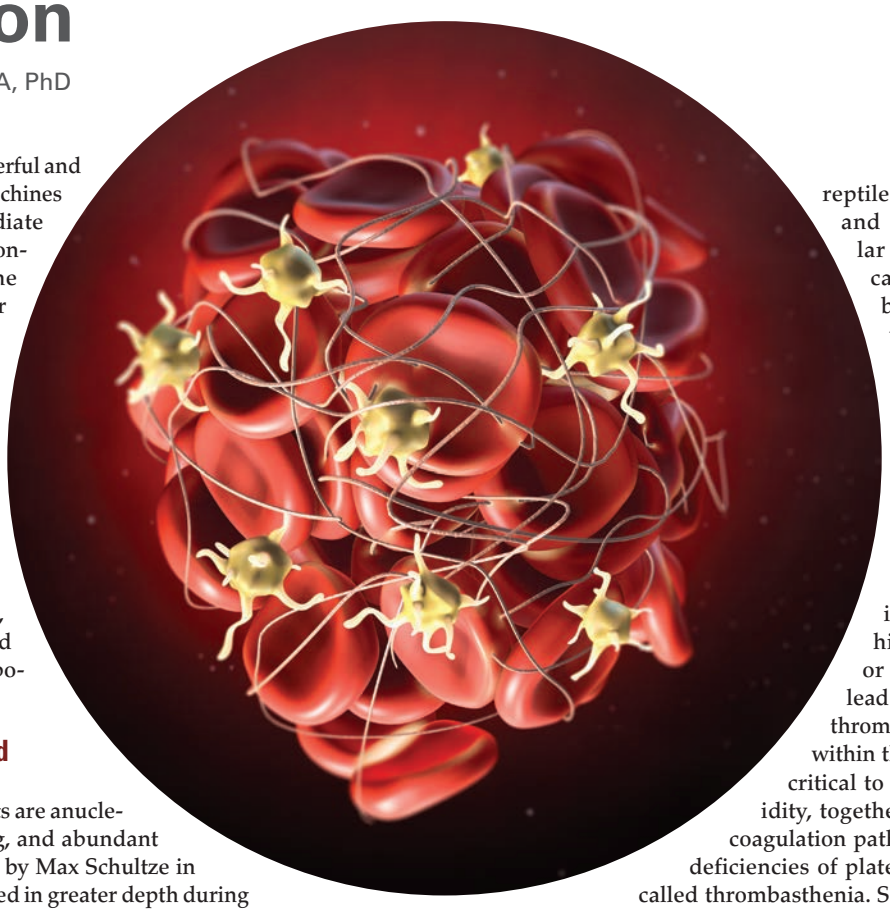
Each center in the network will involve collaborations with peer institutions in the United States and 28 other countries. Research projects will include surveillance studies to identify previously unknown causes of febrile illnesses in humans, find the animal sources of viral or other disease-causing pathogens, and determine what genetic or other changes make these pathogens capable of infecting humans. CREID investigators also will develop reagents and diagnostic assays to improve detection of emerging pathogens and study human immune responses to new or emerging infectious agents. Overall, the breadth of research projects in the CREID network will allow for the study of disease spillover in multiple phases of the process: where pathogens first emerge from an animal host; at the borders between wild and more populated areas, where human-to-human transmission occurs; and, finally, in urban areas, where epidemic spread can occur.

Each center will focus efforts on one or more regions of the world. In Central and South America, for example, studies will include investigations of several arthropod-borne viruses ("arboviruses") including the ones that cause Zika virus disease, chikungunya and dengue. In East and Central Africa, focus pathogens will include Rift Valley fever virus and the coronavirus that causes Middle East respiratory syndrome. In West Africa, in addition to arboviruses, projects are slated on Ebola virus and Lassa virus. In Asia and Southeast Asia, investigators will conduct research on coronaviruses and arboviruses. In every region, investigators will be poised to study any newly emerging pathogen, dubbed "pathogen X."

An award to RTI International in Research Triangle Park, NC, in collaboration with Duke University, Durham, NC, will fund a CREID Coordinating Center. This center will support network activities such as data management, outbreak research response and quality control for biospecimens, assays and reagents. It will also administer a pilot research program for early career investigators.

Methods of testing platelet count and function

By Paul Riley, MBA, PhD



Platelets are powerful and versatile bio-machines serving to mediate clotting in plasma, constantly surveilling the circulatory system for blood loss, acting as a first-line defense to plug holes and stop leaks like a plumber. In addition, platelets also play critical roles in pathogenesis of coronary and thrombotic disorders including strokes, heart attacks, and venous thromboembolism (VTE).

Platelets past and present

In mammals, platelets are anucleate, small circulating, and abundant cells discovered first by Max Schultze in the 1860s but described in greater depth during the 1880s by Italian pathologist Giulio Bizzozero. Platelets were initially described at that time as "discoid corpuscles" containing granules, and distinct from erythrocytes or leukocytes. Initially, scientists referred to them as "piastrine" in Italian, "blutplättchen" in German, and "petites plaques" in French, but later English publications referred to the circulating cell fragments as "platelets."

Platelets develop from large bone marrow cells called megakaryocytes. Following fragmentation, more than 1,000 platelets per megakaryocyte are released. Lower vertebrates including reptiles, amphibians, fish, and birds carry a similar cell in their blood called thrombocytes, but unlike platelets, thrombocytes have nuclei.

Normal platelet counts range between 150,000 – 400,000 per microliter. Low platelet count, or thrombocytopenia, can lead to bleeding symptoms, while high platelet counts, or thrombocytosis can lead to arterial or venous thrombosis. Platelet counts within the normal range are critical to maintain blood fluidity, together with a functional coagulation pathway, but functional deficiencies of platelets can also occur, called thrombasthenia. Several acquired and hereditary disorders can reduce the platelet count, including pregnancy, deficiencies of vitamin B_{12} or folic acid, leukemia, systemic lupus erythematosus, heparin-induced thrombocytopenia (HIT) and thrombotic thrombocytopenic purpura (TTP), among several others.

Patients with bacterial or viral sepsis and the resulting disseminated intravascular coagulation (DIC) also show moderate to severely lower than normal platelet counts, with platelet consumption resulting from the coagulation activation process.[1] Similarly, patients with SARS-CoV-2 infection and confirmed COVID-19 illness display mild to severe thrombocytopenia, depending on the course of the illness. In a study from Wuhan, China, of 1,476 patients with COVID-19, 20.7 percent had thrombocytopenia overall, and thrombocytopenia was more likely in non-survivors compared to survivors. Of the patients with thrombocytopenia, nadir, or trough platelet count of 0-50,000 per microliter was more likely associated with mortality outcome compared to patients with higher platelet counts.[2]

Platelet transfusions are given in patients with low platelet counts (< 50,000 per microliter), such as cancer patients receiving chemotherapy or other patients with low platelet count or platelet dysfunction. However, platelet transfusion is not usually required to prevent bleeding unless the platelet count is < 10,000 per microliter.[3]

Platelet function and activation process

Describing further how platelets function during the activation process, and support hemostasis response to injury, as shown in

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LEARNING OBJECTIVES

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

1) Describe the platelet activation, adhesion, and aggregation process
2) Recall some inherited platelet disorders
3) Describe the types of antiplatelet therapies
4) Discuss the pros and cons of various lab tests to assess platelet count and function

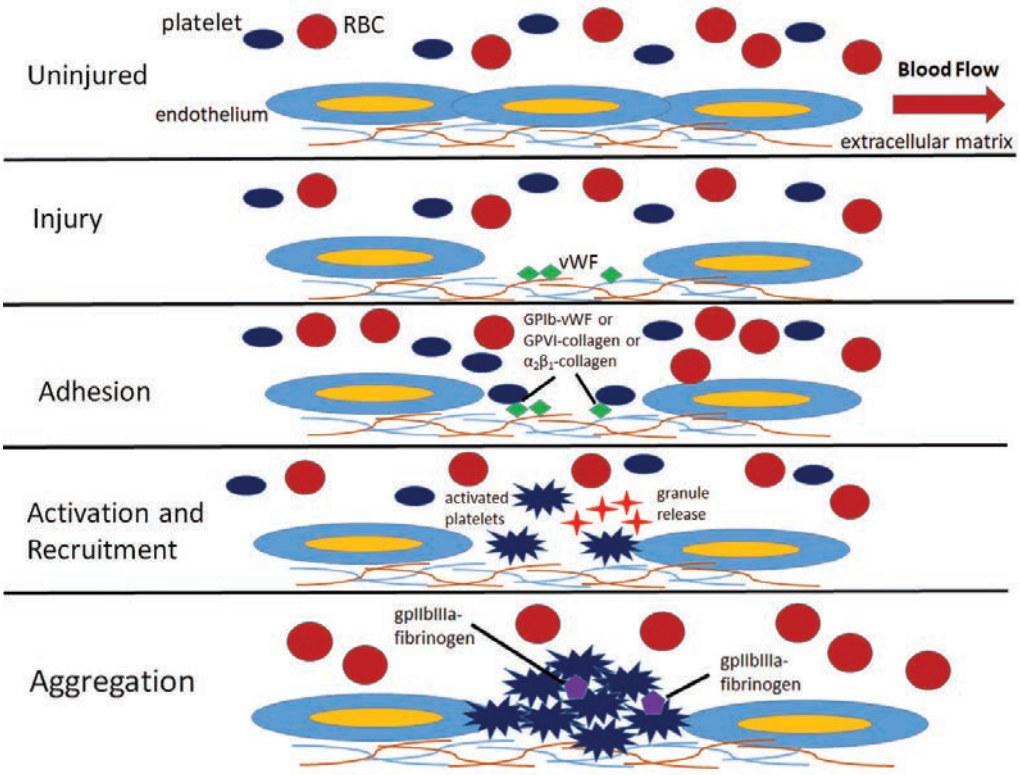

Figure 1: Mechanism of Platelet Activation, Adhesion, and Aggregation

Legend: The process of platelet activation in maintaining hemostasis, starting from the top basal state then proceeding down to the final aggregation outcome. Abbreviations included: red blood cell (RBC), von Willebrand Factor (vWF), glycoprotein (GP).

Figure 1, in an uninjured basal state, platelets are normally in the fluid phase circulating in the blood stream along with erythrocytes, or red blood cells (RBCs), and leukocytes. If tissue injury happens, or if inflammatory processes disturb the endothelial layer, the extracellular matrix containing collagen underlying the endothelial layer will be exposed to the blood flow. The result is binding of von Willebrand Factor (vWF) from the plasma, which then mediates adhesion with platelets flowing in the blood via the GPIb-V-IX-vWF complex. In addition, other platelet receptors mediate adhesion to the collagen in the extracellular matrix, including the GPVI-collagen or $\alpha_2\beta_1$-collagen complexes.

Platelet activation and additional recruitment follows, with simultaneous secretion of contents from α-granules and dense granules containing (among other ingredients) adenosine diphosphate (ADP), serotonin, calcium, and polyphosphates, along with thromboxane A2 (TxA_2). The dense granule contents perform functions not only related to circulating platelet recruitment to the site of injury and mediating hemostasis, wound healing, and infection control, but also play a role in cancer, asthma, sepsis, cardiac hypertrophy, and other disease progression. Indeed, the secretion process constitutes a long lasting, long acting result of platelet activation, and the granule contents play a key role in maintaining vascular integrity, simultaneously helping to maintain health while also aiding disease progression depending on the context.[4]

The last step in platelet activation is aggregation, with the gpIIb/IIIa-fibrinogen complexes helping to cement interactions between the activated platelets within the growing plug. Immediately following the aforementioned steps, and simultaneously during the growth of the platelet plug, the plasmatic, or secondary hemostasis system will start forming the fibrin meshwork and compress the platelet plug. Importantly, the platelet surface serves as an anchor for promotion of the plasmatic coagulation processes *in vivo*, with both the primary and secondary hemostasis processes working together to arrest blood loss. Platelet microparticles or microvesicles shed from activated platelets and megakaryocytes serve to promote coagulation and potential thrombotic effects systemically.

Inherited platelet disorders

The main platelet agonists, or substances producing a physiologic response when bound to certain receptors include TxA_2, along with collagen, thrombin, ADP, and others, resulting in activation, shape changes prior to activation, granule secretion, and aggregation. Aggregation will be deficient when abnormalities of the gpIIb/IIIa complex are present, if there are fibrinogen abnormalities, or if any prior step could not proceed fully. The agonists listed are linked to specific receptors, and when the agonist-receptor combination is absent due to a genetic disorder, or targeted by pharmacologic therapies, platelet activation is downregulated along with any linked downstream pathologic effects.

In patients with one of the many known inherited platelet disorders, deficiencies of one of the previously mentioned agonist-receptor combinations may be present, resulting in bleeding symptoms of varying severity. For example, deficiency of the GPIb complex on the platelet surface is found in patients with Bernard-Soulier syndrome, resulting in giant platelets and lack of binding to subendothelium under high shear stress of normal blood circulation.

Other inherited platelet disorders include 1) Glanzmann thrombasthenia, a lack of gpIIb/IIIa receptor leading to aggregation failure, 2) platelet type von Willebrand Disease, resulting from

GPIb mutations and a lack of binding to vWF, 3) ADP receptor deficiency, in which the anti-P_2Y_{12} receptor is missing from the surface, leading to a lack of response to the ADP stimulus, or 4) deficiency of one of the collagen receptors GPVI or $\alpha_2\beta_1$, leading to loss of platelet adhesion. Last, various platelet granule disorders have been observed, in which a reduction of dense or α-granules results in loss of platelet communication and recruitment.[5]

Antiplatelet therapies

Routine
Platelet Count / Complete Blood Count (CBC)
Blood smear microscopy
Prothrombin Time (PT)
Activated Partial Thromboplastin Time (aPTT)
Thrombin Time (TT)
Fibrinogen
Follow up Tests
Von Willebrand Factor (vWF) Antigen (vWF:Ag) and Activity (e.g. ristocetin cofactor, vWF:RCo, or other methods)
Factor VIII (FVIII)
Platelet Aggregation Studies
Closure Time (CT)
Platelet Reactivity
Viscoelastic Testing (VET) / Thromboelastography (TEG) / Thromboelastometry (TEM)/ sonorheometry?
Light Transmission Aggregation (LTA)
Sendout Tests
Electron Microscopy (EM)
Flow Cytometry
Genetic sequencing

Table 1: Assays for Primary Hemostasis and Platelet Function

Platelet inhibition with one or more antiplatelet medications is required for patients at risk of arterial thrombosis when patients have acute coronary syndrome (ACS), peripheral artery disease (PAD), heart disease, when undergoing percutaneous coronary intervention (PCI) or angioplasty with stent, or stroke prevention following initial occurrence. Several classes of drugs can provide sufficient platelet inhibition in cases of patient risk, including aspirin, targeting the TxA_2 pathway, clopidogrel (Plavix), prasugrel (Effient), and other anti-P_2Y_{12} drugs targeting the ADP pathway, along with abciximab (ReoPro) and other anti-gpIIb/IIIa agents targeting the platelet clumping response.[6]

The goal of antiplatelet therapies is prevention of major adverse cardiovascular events (MACE) in ACS, post-PCI, PAD, or stroke patients by inhibiting platelet shape change and aggregation, making platelets less sticky and less likely to aggregate, thereby, preventing arterial clotting. Platelet reactivity measured by VerifyNow, available for clinical use in various settings, enables determination of whether the aspirin, anti-P_2Y_{12}, or anti-gpIIb/IIIa therapies are effective and to assess patient compliance with therapy. Genetic variability affects metabolism of aspirin and clopidogrel, making the test necessary in certain situations. The test relies on a cartridge-based measurement of aggregation of artificial microbeads covered with fibrinogen in the presence of selected agonists, but is inflexible, and sensitive to platelet count and hematocrit.

Antiplatelet therapies can be confused with anticoagulant, or blood thinning therapy, which targets the secondary hemostasis pathway through inhibition of factor Xa (FXa) or thrombin to prevent or treat venous thromboembolism (VTE). Accordingly, inhibition takes place directly on FXa or thrombin, using small molecule inhibitors such as apixaban or rivaroxaban, or with the help of antithrombin in the case of the unfractionated heparin (UFH) and other related heparinoids.

Assessing platelet count and function

To assess suspected inherited platelet disorders, or to assess effectiveness of antiplatelet therapies, various laboratory methods help clinicians diagnose the underlying disorder and monitor therapies. In the case of inherited disorders, clinicians start with an evaluation of the patient's personal and family history, using the history and physical examination, including assessment of bleeding severity and documenting other potential symptoms related to platelet granule or collagen deficiency, including loss of renal and cardiac function, hearing loss, or facial dysmorphism.[7]

First line laboratory testing in the context of primary hemostasis testing and identification of potential inherited or acquired platelet disorders involves platelet count determination, commonly performed in a complete blood count (CBC) measurement on an automated hematology analyzer. The hematology analyzer will also give the mean platelet volume (MPV), with high MPV indicating potential platelet overproduction, or providing a warning sign of cancer presence, but also associated with hyperthyroidism, heart disease, diabetes, vitamin D deficiency, stroke, atrial fibrillation, or high blood pressure.

Although hematology studies provide rapid and precise information on platelet count and MPV, there is no information about platelet function, and accuracy may be decreased at low platelet levels. Microscopy performed simultaneously will assist with identification of morphological issues with platelets or other blood cells.

Other routine screening tests include coagulation tests prothrombin time (PT), activated partial thromboplastin time (aPTT), fibrinogen, and thrombin time (TT), as shown in Table 1. The coagulation tests allow for ruling out coagulation factor deficiencies, including fibrinogen levels or function. Von Willebrand Factor (vWF) antigen and activity testing provides information about vWF levels or function linked to platelet activity. If vWF antigen levels are decreased, factor VIII (FVIII) levels are often simultaneously decreased since vWF and FVIII are linked together in the plasma to enhance stability and half-life of both proteins. The coagulation tests will commonly be performed on an automated coagulation analyzer, but lack information about platelet function, so coagulation parameters may all be normal in patients with platelet disorders.

Depending on the results of the screening tests, various follow-up tests will be performed depending on equipment available and local practices. Closure time (CT) under high-shear stress performed on a PFA-100 is widely available and assists with identification of platelet or vWF issues, or reflecting anticoagulant drug presence, but the assay is relatively inflexible and sensitive to platelet count and hematocrit variation. Viscoelastic tests (VET) – including thromboelastography (TEG), rotational thromboelastometry (ROTEM), and SEER (Sonic Estimation of Elasticity via Resonance) sonorheometry – allow for investigation of platelet function. VET platforms have the advantage of being available in various clinical settings, including not only central laboratories but also at the point of care.

Various VET methods assess whole blood clotting, providing information on the platelet contribution to clot stiffness and platelet dysfunction, and assist with platelet function analysis along with

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guiding transfusion during surgeries or emergency procedures. Further, SEER sonorheometry is the only viscoelastic test that directly measures and reports quantification of the platelet contribution to clot stiffness.[8] However, VET platforms are not sufficiently sensitive to all functional platelet deficiencies, requiring use of additional tests for a complete diagnosis.

Confirmatory methods for platelet function analysis

Light transmission aggregation (LTA) using platelet rich plasma (PRP) tracks change in light transmission through a sample after stimulation with a panel of various agonists. LTA is the cornerstone and gold standard for platelet function investigation due to the wide panel of agonists used and sensitivity to all inherited and acquired disorders. Disadvantages of LTA include poor standardization, non-automated techniques, and stringent requirements for sample processing and platelet count. Briefly, the mixture of PRP and the selected agonist is stirred to ensure adequate mixing and collision of platelets in the sample, while also preventing sedimentation of platelets. Aggregation is initiated by the addition of an agonist, including ADP for analysis of the P_2Y_{12} and P_2Y_1 pathways, arachidonic acid and epinephrine for investigation of the TxA_2 pathway, collagen for activation of the GPVI-collagen or $\alpha_2\beta_1$ receptors, thrombin receptor activation peptide-6 (TRAP-6) for analysis of the thrombin pathway, and ristocetin to induce potential vWF binding to platelets in the sample.

The agonist added to the sample results in LT increase, and a normal result is obtained if LT reaches the 100 percent level set with the platelet poor plasma (PPP) control. Further analysis of the shape and kinetics of the aggregation curve gives additional information on granule secretion and shape changes indicating various deficiencies. Guidelines from the Clinical Laboratory Standards Institute (CLSI) and the *American Journal of Clinical Pathology* are available for laboratories that want to implement LTA.[9,10]

Performing further send out tests for suspected primary hemostasis and platelet disorders is critical to determine the exact diagnosis and tailor treatment accordingly. To assess potential granule deficiencies or problems with other internal structures, scanning electron microscopy (SEM) or transmission electron microscopy (TEM) enables highly sensitive analysis of internal issues, but the equipment and expertise needed are not widely available, and the procedures are time consuming.

As part of the confirmatory process, other send out tests are performed, including flow cytometry using specific antibodies on a small sample size to analyze the number and function of the various activation markers on the platelet surface, along with response to various agonists, even when the platelet count is low. Finally, genetic sequencing procedures will determine the exact mutation responsible for the disorder, giving the clinician sufficient information to manage the patients on a long-term basis.

With the vital contribution of platelets to the overall hemostasis process, and their involvement in many inherited and acquired disease states, it is important that laboratories and clinicians recognize abnormal screening tests indicating potential platelet issues requiring further investigation. Although the method has inherent challenges, LTA occupies a considerable place in platelet disorder diagnosis and monitoring, ensuring placement in laboratory medicine now and in the future.

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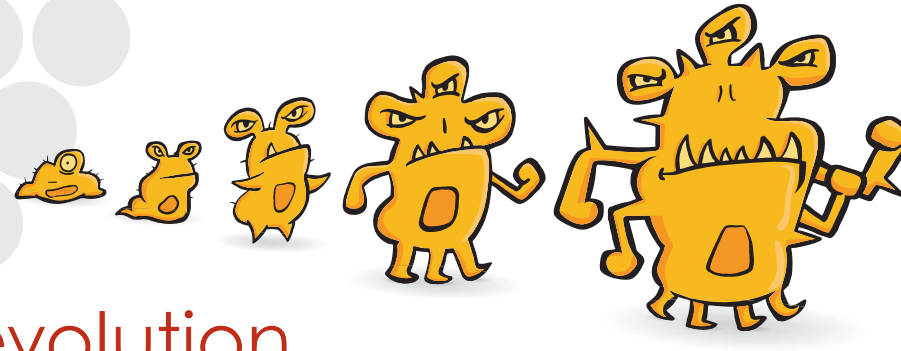

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Methods of testing platelet count and function

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TEST QUESTIONS

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1. **Platelets develop from large_____ called megakaryocytes. Following fragmentation, more than 1,000 platelets per megakaryocyte are released.**
   - A. bone marrow cells
   - B. red blood cells
   - C. white blood cells
   - D. T cells

2. **Low platelet count, or thrombocytopenia, can lead to _____, while high platelet counts, or thrombocytosis, can lead to arterial or venous thrombosis.**
   - A. blood clotting issues
   - B. bleeding symptoms
   - C. dizziness
   - D. shortness of breath

3. **Several acquired and hereditary disorders can reduce the platelet count, including pregnancy, deficiencies of vitamin B12 or folic acid, leukemia, _____ , heparin-induced thrombocytopenia (HIT), and thrombotic thrombocytopenic purpura (TTP), among several others.**
   - A. multiple sclerosis
   - B. vasculitis
   - C. systemic lupus erythematosus
   - D. anemia

4. **Patients with bacterial or viral sepsis and the resulting disseminated intravascular coagulation (DIC) also show moderate to severely higher-than-normal platelet counts, with platelet consumption resulting from the coagulation activation process.**
   - A. True
   - B. False

5. **In patients with bacterial or viral sepsis, platelet transfusion is not usually required to prevent bleeding unless the platelet count is _____.**
   - A. <6,0000 per microliter
   - B. <10,000 per microliter
   - C. <15,000 per microliter
   - D. <20,000 per microliter

6. **If tissue injury happens, or if inflammatory processes disturb the endothelial layer, the extracellular matrix containing _____underlying the endothelial layer will be exposed to the blood flow.**
   - A. collagen
   - B. carbohydrates
   - C. plasma membrane
   - D. polysaccharide

7. **The last step in platelet activation is aggregation with the gpIIb/IIIa-fibrinogen complexes helping to cement interactions between the activated platelets within the growing plug.**
   - A. True
   - B. False

8. **Platelet microparticles or microvesicles shed from activated platelets and megakaryocytes serve to slow down coagulation.**
   - A. True
   - B. False

9. **Platelet agonists are linked to specific receptors, and when the agonist-receptor combination is _____due to a genetic disorder, or targeted by pharmacologic therapies, platelet activation is downregulated along with any linked downstream pathologic effects.**
   - A. aggravated
   - B. over stimulated
   - C. absent
   - D. damaged

10. **Platelet inhibition with one or more antiplatelet medications is required for patients at risk of arterial thrombosis when patients have acute coronary syndrome (ACS) peripheral artery disease (PAD), ____, when undergoing percutaneous coronary intervention (PCI), or angioplasty with stent, or _____ following initial occurrence.**
    - A. heart disease, stroke prevention
    - B. heart disease, aneurysm
    - C. aneurysm, stroke prevention
    - D. cancer, heart disease

11. **____variability affects metabolism of aspirin and clopidogrel, making the test necessary in certain situations.**
    - A. disease
    - B. symptom
    - C. genetic
    - D. dosage

12. **To assess suspected inherited platelet disorders, or to assess effectiveness of antiplatelet therapies, various laboratory methods help clinicians diagnose the underlying disorder and monitor therapies.**
    - A. True
    - B. False

13. **First line laboratory testing in the context of primary hemostasis testing and identification of potential inherited or acquired platelet disorders involves platelet count determination, commonly performed in a _____ measurement on an automated hematology analyzer.**
    - A. hemoglobin
    - B. coagulation
    - C. white blood cell
    - D. complete blood count (CBC)

14. **Although hematology studies provide rapid and precise information on platelet count and MPV, there is no information about platelet function, and accuracy may be decreased at _____ platelet levels.**
    - A. high
    - B. low
    - C. moderate
    - D. all of the above

15. **If vWF antigen levels are _____, factor VIII (FVIII) levels are often simultaneously _____ since vWF and FVIII are linked together in the plasma to enhance stability and half-life of both proteins.**
    - A. increased; increased
    - B. decreased; decreased
    - C. increased; decreased
    - D. decreased; increased

16. **Viscoelastic test (VET) platforms are not sufficiently sensitive to all functional _____ deficiencies, requiring use of additional tests for a complete diagnosis.**
    - A. plasma
    - B. white blood cell
    - C. red blood cell
    - D. platelet

17. **Light transmission aggregation (LTA) is the cornerstone and gold standard for platelet function investigation due to the _____ used and sensitivity to all inherited and acquired disorders.**
    - A. wide panel of agonists
    - B. variety of anti-clotting agents
    - C. pre-analytic variables
    - D. analytic variables

18. **Disadvantages of light transmission aggregation (LTA) include poor standardization, _____ and stringent requirements for sample processing and platelet count.**
    - A. use of whole blood
    - B. non-automated techniques
    - C. use of small sample volume
    - D. use of red and white blood cells

19. **In LTA, agonist added to the sample results in LT increase, and a normal result is obtained if LT reaches the _____ level set with the platelet poor plasma (PPP) control.**
    - A. 25 percent
    - B. 50 percent
    - C. 75 percent
    - D. 100 percent

20. **To assess potential granule deficiencies or problems with other internal structures, scanning electron microscopy (SEM) or transmission electron microscopy (TEM) enables highly sensitive analysis of internal issues, the equipment and expertise needed are widely available, and the procedures are simple and easy to perform.**
    - A. True
    - B. False

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Key challenges of training for lab safety and COVID-19 effects

By Brenda Silva

Traditionally, best practices in lab safety have included wearing personal protective equipment (PPE) while performing lab procedures in such a way as to prevent the risk of injury or transmission of infectious diseases to lab personnel. Today, lab safety includes the same practices plus new issues and challenges that lab directors must address, such as hiring and training a sufficient number of incoming lab personnel to replace staff members who are aging out into retirement.

Along with ensuring necessary workforce positional needs are met, training and proficiency of all new lab personnel are top priorities, just as in the past. However, with the emergence of SARS-CoV-2 and COVID-19, current learning curves in clinical labs also must incorporate procedural proficiencies that prepare all lab staff in the event of another pandemic in the future.

Lab workforce shortage

Before lab directors create or streamline training programs for additional lab personnel, their work begins with finding qualified candidates to fill key positions within the clinical lab. Current research highlights a workforce shortage among lab personnel, with some positions left unfilled for months.[1]

Brittany Vaughn, MHA, MLS(ASCP)SM, Global Healthcare Consultant at BD, located in Franklin Lakes, NJ, reports that "Laboratories are experiencing staffing vacancy rates that exceed the number of new graduates; coupled with high retirement rates due to an aging working population, this creates a substantial workforce shortage crisis."[1]

She continued, "The workforce profile of many laboratories looks like an inverted bell curve, with a large number of technologists just starting out their career and an even larger number of highly experienced technologists preparing for retirement in the next five to 10 years. As those retirement-ready technologists move on to their next stage of life, labs commonly face challenges finding and hiring experienced and qualified replacements. It is not uncommon for certified laboratory positions to go unfilled for months due to this workforce shortage, particularly those seeking a degree of specialty experience or positioned on less-desirable overnight shifts."

Effective training and proficiency

For labs fortunate enough to find qualified additions to their staff, the most important task at hand becomes training them. Training programs, regardless of the area of specialty, are typically only as successful as the communication of an instructor and the competence of a student. In the clinical lab, both instructor and student look to their training for safety within the lab and for helping patients waiting for a diagnosis.

Luann Ochs, MS, Product Development Manager at the Clinical and Laboratory Standards Institute (CLSI), located in Wayne, PA, pointed out that "Proper training of laboratory workers is essential to producing accurate results for patient care and is the lab's first line of defense against errors. Robust training and competence assessment programs are an essential element of a quality management system and are required by all laboratory accreditors. Although laboratory managers know the importance of training for good quality results, competence assessment is one of the top 10 deficiencies seen by major accreditors in the U.S.[2] Clearly, for many laboratories, more work needs to be done in this area."

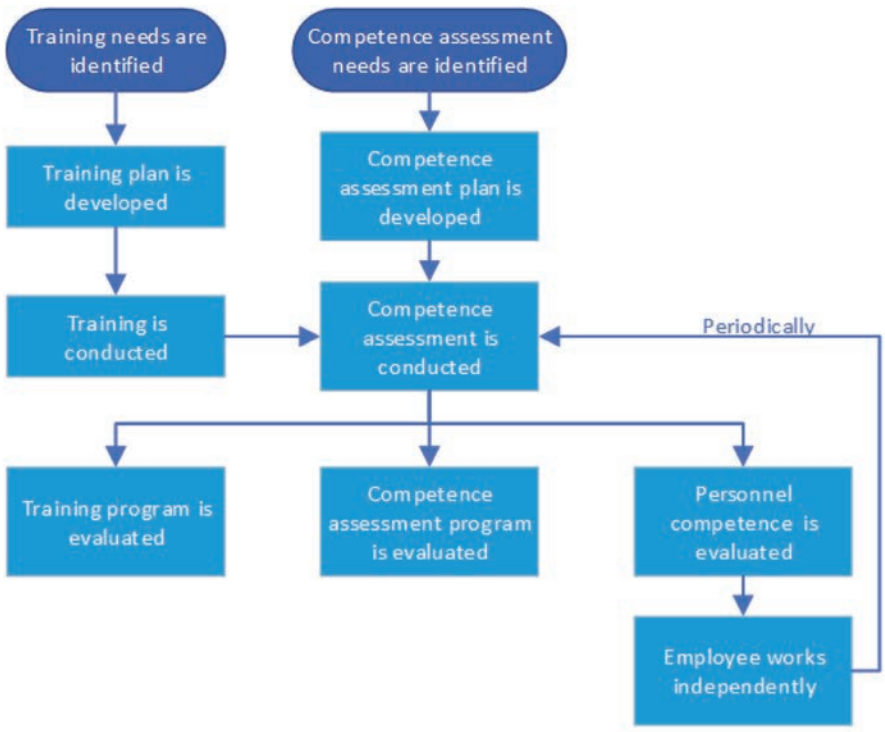

Figure 1: The inter-relationships between training and competence assessment
Source: CLSI

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Training and competence assessment

According to CLSI's document QMS03, *Training and Competence Assessment*,[3] "people are the most valuable resource of the organization. Effective training and competence assessment programs ensure personnel are knowledgeable and competent in their assigned roles and responsibilities."

As such, the QM303 CLSI document lists three recommendations for effective training and competence assessment programs:

- Ensure personnel performance results in consistent, predictable, and high-quality outcomes.
- Ensure performance of assigned job tasks remains constant.
- Verify that personnel have and can demonstrate the necessary knowledge, skills, and behaviors to perform their respective duties.

Ochs adds, "And while everyone knows that training is needed for newly hired personnel, it's also important to ensure effective training whenever organizational or technological changes occur that affect work processes, and when any employee repeatedly demonstrates performance problems. Competence should be assessed not only following a training exercise, but also periodically to ensure continued performance. Competence should also be assessed when processes or responsibilities change, as well as when any retraining needs are identified."

According to the QMS03, "an effective training and competence assessment program can decrease the risk of a nonconforming event that could lead to an undesired patient outcome and could also have adverse financial consequences."

Challenges of training methods

When it comes to the best training methods for lab personnel, all staff members may not respond the same way to the same methods. It is up to the lab manager to realize this and work with new hires to find a training method that allows the required training to take place in a way that benefits both the lab manager and the new staff member.

Vaughn from BD asserts, "Hiring new graduates and trainable individuals can be a prerequisite for a steeper learning curve, resulting in increased training efforts, which more often than not are short cut due to a lack of time due to the staffing challenges. There are, however, a couple of different approaches available in a laboratory manager's toolbox to counteract this downward spiral:

- Defining a clear career pathway for non-certified employees within the lab to encourage advancement into a technologist role through partnership with an MLS or MLT teaching program, or by providing an opportunity to gain the necessary full-time clinical experience required to qualify for alternate certification routes through the American Society for Clinical Pathology (ASCP). The respective employees would contractually guarantee to remain employed by the laboratory for a set amount of years, if the laboratory sponsors their education. Having defined career pathways can create a steady feed of employees to pull from as retirements and other openings present themselves.
  - (When considering this approach, it is important for laboratories to support their employees by providing access to education and training for the scientific theory behind the work they are doing as well as teaching how the work performed ties into the greater picture of patient care.)
- Adopting new automated technology in the laboratory will free up resources to be reallocated into full- or part-time training roles, allowing for greater and more focused attention on the training process.
- Bringing experienced technologists back after retirement, or incentivizing them to stay on longer prior to retirement, by offering part-time training roles to bridge the knowledge gap and allow them to pass on the baton.
- Exploring new training methods that allow the trainees to access training content from their mobile devices will appeal to different training styles, as well as allow the trainings to be executed more frequently. Video-recorded training is a successful method for ensuring consistency of material shared with students."

> "Proper training of laboratory workers is essential to producing accurate results for patient care and is the lab's first line of defense against errors."
> -- Luann Ochs, MS

Effects of COVID-19 on lab safety

With almost a year of dealing with SARS-CoV-2 and COVID-19 on a daily basis, it would seem that lab personnel have a good understanding of the virus and its subsequent disease. However, the reality is that there is still much to learn from this pandemic that continues to be responsible for infections and deaths every day around the world.

Reminding clinicians about the risk of COVID-19 transmission, CLSI's Ochs points out that "Although the general transmission of COVID-19 is typically through respiratory droplets, laboratory workers are at risk of infection through aerosolization, splattering, and splashing of laboratory specimens. This can occur whenever samples are being handled, but especially when samples are being opened and prepared for testing. Precautions must be taken to prevent exposure from accidental sample contact."

According to another CLSI document, M29, *Protection of Laboratory Workers From Occupationally Acquired Infections*, "facial barrier protection should be used if there is a reasonably anticipated potential for splattering or splashing blood or body substances or any liquid suspected of containing infectious agents." It goes on to say that "a plastic face shield provides the best facial protection,"[4] and that splashguards may serve as an acceptable alternative to plastic face shields, but neither face shields nor splashguards are protective enough when it comes to aerosols. When aerosols are a concern, respirators are needed, or all work can be performed

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Ochs summarizes, "The M29 guideline encourages labs to be prepared for dealing with infectious agents by preparing a biological hazard assessment before a hazard actually occurs. Factors to consider include possible routes of transmission, including portals of entry through which pathogens can enter the body; possible agents that could be encountered and their pathogenicity; and the work environment, including the facility, procedures, and the availability and use of PPE. All of these factors contribute to the overall level of hazard to which an individual laboratory worker may be exposed."

"In addition, according to M29, negative factors in the laboratory environment can affect the behavior of staff (e.g., poor workflow, poor housekeeping, insufficient space in the BSC). The nature of the work itself (e.g., high stress, high volumes of samples and workload, lack of time for adequate training or attainment of competency, repetitive nature of routine procedures) can lead to a false perception of safety. This perception can lead to complacency and unknowingly increase the risk of exposure (e.g., disruption of air barrier in the BSC, assumptions that PPE are performing properly),[4] she added.

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CLSI currently offers the following documents on its website to help with the COVID-19 pandemic. The documents are free of charge and only require an email to download. Once logged in, a summary of the documents is available, with each description including a "How is this helpful for COVID-19?" tip. Further information can be found here: https://clsi-covid-19.org/Login.aspx.

CLSI EP19 ED2:2015

A Framework for Using CLSI Documents to Evaluate Clinical Laboratory Measurement Procedures, 2nd Edition

This report uses the "measurement procedure lifecycle" framework to aid users of CLSI evaluation protocols documents during establishment and implementation of measurement procedures developed by both commercial manufacturers and clinical laboratories, i.e., for laboratory-developed tests.

How is this helpful for COVID-19?

EP19 explains when you need to validate a test and when you need to verify a test. It also lists all CLSI documents that can help you either verify or validate a new test in your laboratory.

CLSI GP36 A:2014

Planning for Laboratory Operations During a Disaster; Approved Guideline

This document provides guidance for laboratory and healthcare leadership for development, implementation, and sustainment of effective emergency preparedness plans (all hazards) supporting nonanalytical components of clinical and public health laboratory services that may pertain to various natural and manmade disasters.

How is this helpful for COVID-19?

This document will help you develop and implement emergency preparedness plans.

CLSI MM22 A:2014

Microarrays for Diagnosis and Monitoring of Infectious Diseases; Approved Guideline

This document provides guidance for the laboratory development and use of qualitative nucleic acid microarray methods for the diagnosis and monitoring of infectious diseases. It also presents recommendations for validation and verification, quality control, and interpretation of results.

How is this helpful for COVID-19?

This guideline will help you understand how to validate or verify a new microarray test.

CLSI POCT07 A:2010

Quality Management: Approaches to Reducing Errors at the Point of Care; Approved Guideline

This document presents the core infrastructure for a standardized error tracking system with the primary goals of reducing risk and increasing quality of point-of-care testing, while accumulating standardized data for benchmarking use.

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CLSI QSRLDT-2015

Quality System Regulation for Laboratory-Developed Tests: A Practical Guide for the Laboratory

This practical guide, compiled with the help of experts from the in vitro diagnostics industry, is intended for the laboratory that is creating laboratory developed tests that may be subject to the U.S. Food and Drug Administration (FDA) regulations, specifically the Quality System Regulation (QSReg), 21 CFR Part 820.

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Match Test Menu to Need

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Chem 8, Hb and Hct Menu

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Blood Gases, Lactate Menu

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Lab information is a key ingredient in population health

By Linda Wilson

Laboratories provide crucial data in in the diagnosis and treatment of diseases. That is why industry leaders think lab managers should be involved in plotting their institution's transition from payment structures based on the volume of services delivered to those based on patient outcomes.

Myra Wilkerson, MD
Courtesy of Geisinger Health System

"We own so much of the quantitative objective data that is generated in healthcare, so how do we help build the evidence base that helps prove that what we are doing for patients in terms of testing actually helps achieve positive outcomes in their overall health and their overall care? To me, the whole crux of it is moving from fee-for-service to value-based care that focuses on the value to the patient, and how we build the evidence to support our case," explained Myra Wilkerson, MD, Chair of Laboratory Medicine at Geisinger Health System, Danville, PA.

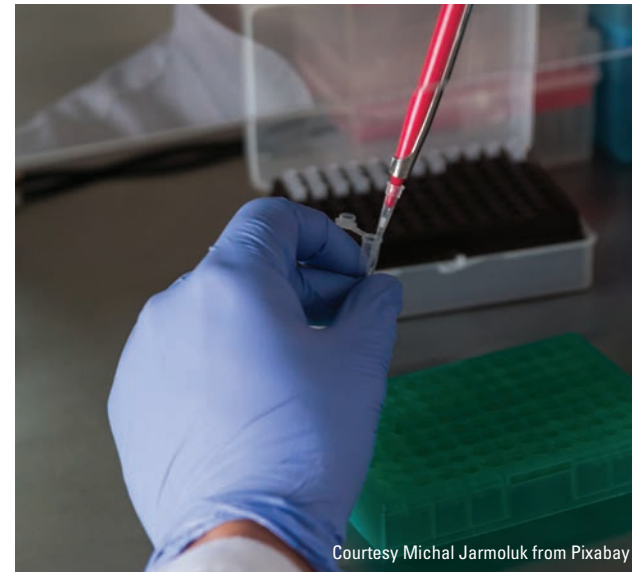
Karen Kaul, MD, PhD
Courtesy of NorthShore University HealthSystem

Karen Kaul, MD, PhD, Chair of the Department of Pathology and Laboratory Medicine at NorthShore University HealthSystem, noted that the new approach requires a change in mindset. "Historically, physicians order individual lab tests, and they get that result back and they look at that result. That is how we interpret lab tests. We are now looking at new and innovative ways to use lab data so there is more than just the one-lab-test-at-a-time approach."

Wilkerson and Kaul are not alone. The Project Santa Fe Foundation, where Wilkerson and Kaul are board members, was launched in 2016 to promote the role and value of laboratories – and their data – in the healthcare industry's transition to reimbursement based on outcomes.

"It is really about inserting our managers and our pathologists into the care team – just as pharmacy has become an integral part of the care team, particularly in the inpatient setting," Wilkerson said.

In an article in *Academic Pathology*, the group pointed to the role lab tests play in both inpatient and outpatient treatments. They argued that labs can play a central role in the transition to value-based care through such activities as promoting appropriate test utilization, interpreting test results and guiding subsequent clinical actions, and optimizing the use of test data and pathology reports in analytics.[1]



Courtesy Michal Jarmoluk from Pixabay

Laboratory information plays an important role in the healthcare industry's transition to value-based care because it comprises a large chunk of the clinical data in electronic health records.

They explain this transition in the lab's role within the health system as moving from Clinical Lab 1.0 to Clinical Lab 2.0 – or from reactive to proactive.

Michelle Del Guercio, Vice President of Marketing, Sunquest Information Systems, added that, "This also will help position the lab to be seen as a strategic asset, align it to receive funding as a part of these initiatives, and continue to increase its value to the organization."

How should lab managers become involved?

The first step is to understand what the health system's key strategic initiatives are to drive the transition to value-based care. Some examples include population health, which involves improving the health outcomes for groups of similar patients, such as those with diabetes, and chronic disease management, which involves actively monitoring and educating individual patients to help them manage their health.

The role of data

Second, they should recognize that "the bulk of the medical record data (70 percent or so) is coming from the laboratory, and these are all quantitative results that can be used to get a really good sense of population health and also on an individual basis," Suren Avunjian, CEO of LigoLab Information System, said, citing an often-quoted statistic.

Del Guercio said, "Supporting population health requires sophisticated reporting, connectivity and systems integration. This is especially true for complex cases that require extensive lab testing, such as congestive heart failure, pneumonia, acute cardiac disease, infections and chronic kidney disease."

In addition to patient-level data, lab results, either alone or combined with other patient data from other sources, provide insights into how to improve outcomes at the population level.

For example, longitudinal lab results are important ingredients in electronic models that risk-stratify patients with chronic conditions. Based on the output from the models, clinicians know

which of their patients need attention, such as from a care coordinator, to help prevent costly hospital stays and ED visits.

"There are incredible benefits from harnessing the patient data produced not only in the lab but throughout the hospital," said David Metrena, Vice President, Healthcare, at LabVantage Solutions, adding, "Being able to analyze and model data under different circumstances, or do some predictive analytics, enables a much broader view of the population being served."

Interoperability challenges

However, problems with sharing data between laboratory information systems (LIS) and electronic health records (EHR) can impede the data aggregation and analysis necessary to support population health and disease management efforts.

"In an ideal scenario, there is EHR/LIS integration, and all that data, including claims data, is within a data warehouse where it can be compiled and accessed for any type of query needed to support population health initiatives. But this scenario is certainly not the norm," said Kim Futrell, MT(ASCP), MSHI, Products Marketing Manager at Orchard Software.

The issues often are caused by disparities in the way different systems manage patient identification, test codes, diagnosis codes and other data elements.

Issues with interoperability can be magnified at health systems that have more than one EHR in addition to a LIS and/or other sources of patient data, such as wireless patient-monitors.

In those instances, it may make more sense to stream the data from the EHRs, LIS and other sources into a separate data warehouse for analytics, Futrell said.

Widespread industry adoption of standardized programming interfaces, or APIs, can help remedy interoperability problems. One prominent standard is Fast Healthcare Interoperability Resources (FHIR) framework, which was developed by HL-7 International, a nonprofit standards-developing organization. In a 2019 blog post, the Office of the National Coordinator for Health Information Technology (ONC) said about 32 percent of EHR vendors were incorporating FHIR into their platforms; however, the 10 largest EHR vendors all reported using FHIR.[2]

And in final rules released earlier this year, ONC and the Centers for Medicare & Medicaid Services (CMS) require vendors to use standardized APIs for patient data, saying the ultimate goal is for patients to have easy access to their electronic medical information.

Geisinger's population health efforts

Issues with data interoperability have not prevented Geisinger's laboratory managers from participating in numerous value-based care projects to improve clinical outcomes.

One example is the inpatient sepsis bundle. In 2014, Geisinger created a multidisciplinary team, including lab, to improve sepsis diagnosis for patients in the emergency department. As a result of that effort, Geisinger decided to move the testing and analysis of blood cultures to the local hospital lab, instead of the integrated health system's core laboratory.

Now, all hospitals and micro-hospitals (freestanding emergency departments with a small number of beds) process the blood samples. "Most of our laboratories have a pneumatic tube system that delivers the bottles from the emergency room. If they don't, there are couriers," explained Donna Wolk, MHA, PhD, [ABMM] Division Director of Molecular and Microbial Diagnostics in Laboratory Medicine at Geisinger.

The blood samples are incubated on-site. For positive cultures, gram stains and multiplex PCR to identify the

microorganism also are done locally. Antimicrobial susceptibility testing is then completed at the core lab.

With this process, Geisinger has reduced the time required to identify an organism and determine what the appropriate antibiotic is by about 10 hours and has a positive culture grown within seven hours. Noting that blood samples are sometimes shipped long distances, Wolk said those turnaround times are "unheard of if you are already transporting the bottle six or seven hours. You have missed the early window to get the physician that extra information to tailor antimicrobials appropriately."

But those time savings will not improve patient outcomes unless ICU providers use the information to prescribe the appropriate antibiotic. That is why Geisinger's lab employees send an encrypted text message to the provider with the organism's identification, Wolk said.

Expanding to outpatient operations

Geisinger also has expanded its sepsis work to the outpatient arena. The goal is to develop a model to identify patients who are at risk of developing sepsis within two or three months. The long-term goal would be to incorporate the model into the EHR at the point of care, so that primary care providers can intervene to prevent patients' health from deteriorating to the point that they develop sepsis.

That goal is not a reality at this point. Currently, a team at Geisinger is sifting through thousands of data points, such as test results and co-morbidities, to determine the factors associated with risk for developing sepsis.

More recently, the lab has been involved in in efforts to improve patient care for anemia."At any given time, somewhere around 10 or 15 percent of your population is anemic. It is a co-morbidity of so many chronic diseases – COPD, congestive heart failure, and chronic renal disease," Wilkerson said.

Geisinger reengineered the process so that physicians can order a CBC anemia reflex panel, instead of the CBC panel at one office visit followed by an anemia reflex plan at the next visit.

With the new process, the lab automatically runs tests to determine the root cause of anemia on samples that are positive. "That saves the patient a lot of work up and can save several months of time and unnecessary appointments getting to a diagnosis," Wilkerson said.

The process has been pilot-tested at several locations and Geisinger is analyzing the data to quantify the results. Based on anecdotal reports alone, Wilkerson said that both patients and providers are happy with the streamlined process.

NorthShore's efforts

Meanwhile, NorthShore University HealthSystem, located on Chicago's suburban North Shore, also has been using lab data in innovative ways to help physicians diagnose and treat patients.

One example is an app called What's Going Around? Updated nightly, the app displays a map with the rates of various infectious diseases and pediatric asthma in the health system's local service area. Providers access the electronic program either by downloading the app to their mobile device or clicking on an icon on the home screen of the EHR.

In addition to asthma, the other diseases tracked in the app include influenza, strep, whooping cough and gastroenteritis.

"We used to very proudly publish our weekly rates of flu on our website, but it wasn't in the hands of physicians when they needed it," Kaul said. With the app, "We are taking the data and getting it out there for them. It has been quite useful."

The members of Project Santa Fe also are collaborating on projects. For example, multiple organizations are involved in a pre- and post- intervention study to find out if the improvements Geisinger has logged in the time to identify a bacteria and appropriate antibiotic can be replicated at other institutions, Wolk said.

In summing up the lab industry's role in value-based care and population health efforts, Wilkerson said, "We have to become stewards of that data. We have to learn how to manipulate that data, we have to learn how to manage that data, and we have to learn how to ask the right questions of that data."

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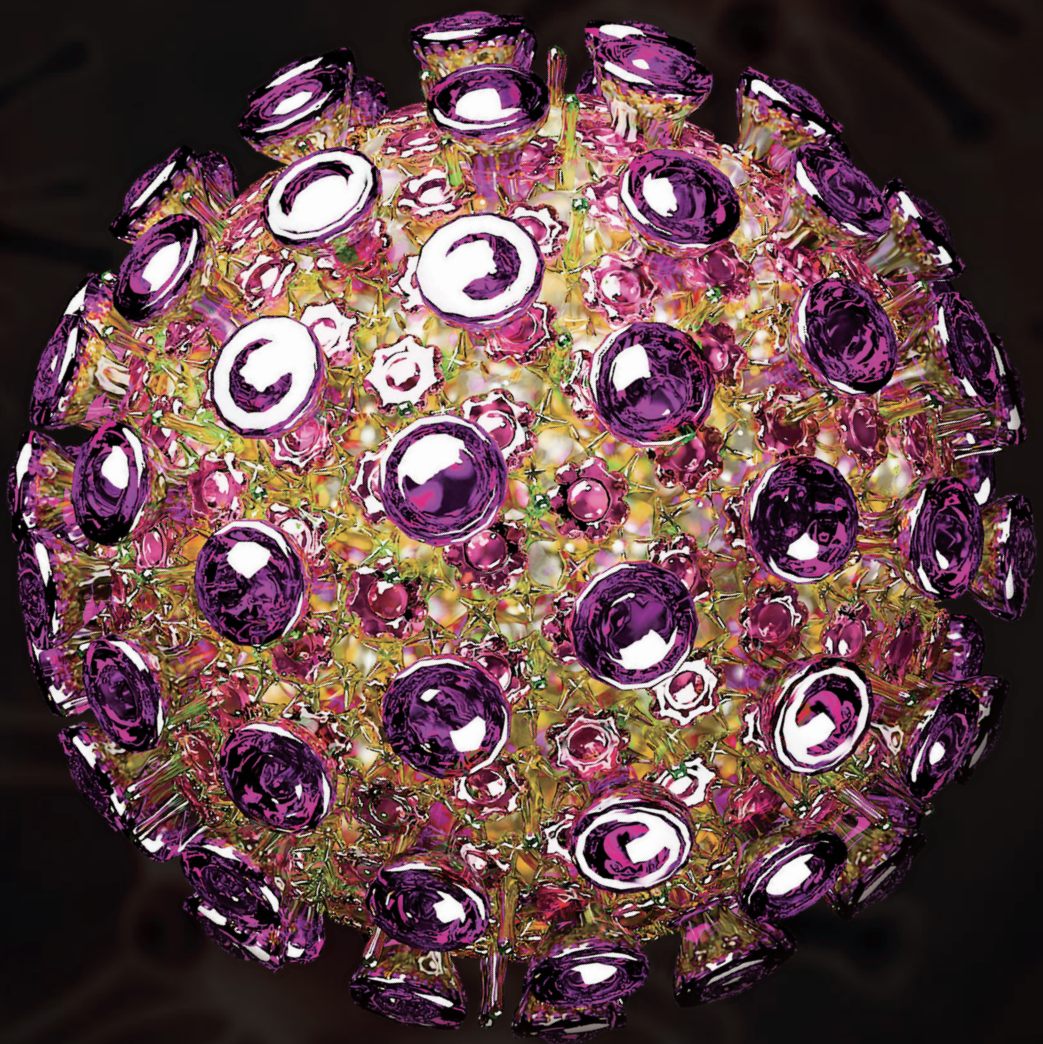

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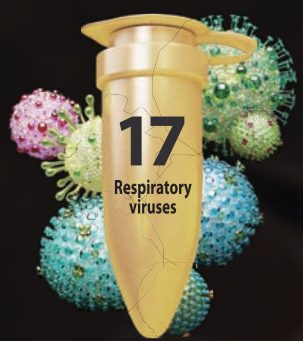

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Changes in clinical lab industry dictate changing trends in analyzers

By Brenda Silva

When faced with new disease challenges, clinical laboratorians have typically managed to meet the diagnostic test needs for patients. With the emergence of the COVID-19 virus, manufacturers have quickly adapted their analyzers to keep pace with increased testing demands, and they have adopted new approaches that can accommodate changing test requirements.

General analyzer trends

Aside from diagnostic trends that are specific to COVID-19 detection, other rising analyzer trends in the clinical lab industry focus on time-saving and cost-effective features, designed to improve efficiency while increasing test throughput.

Venita Shirley, Director of Marketing, North America Commercial Operations at Instrumentation Laboratory, located in Bedford, MA, reported, "Liquid, ready-to-use reagents with long on-board stabilities have become a requirement in most labs today. With reagents that are ready to use and feature long on-board stability (10 days for PT and APTT) there is less waste, less cost and less time spent on non-testing activities. Plus, incorrect reconstitution of reagents is often the most common issue with out-of-range QC."

Adding to Shirley's point about less waste, German Nunez, Marketing Manager, Core Business at Dynex Technologies, located in Chantilly, VA, said, "A trend we're seeing is multiplexing or getting multiple results from a single-reaction vial."

Analyzer trends and COVID-19

The COVID-19 virus has created heavy testing demands that require labs to process thousands of swab tests in record turnaround times in order to identify positive cases and stave off additional infections.

At the same time, many existing analyzer features have experienced increased usage because of COVID-19 demands, such as automated ELISA processing, according to Nunez, as well as features related to hemostasis, according to Shirley.

"The most requested feature is to fully automate hemostasis testing through the implementation of hemostasis work cells. With a hemostasis work cell, the sample processing and routing is automatic and standardized, freeing up techs to perform more critical functions. Labs with specific work cells have improved their STAT turn-around-times (TATs) and have standardized the time to result for the rest of the workload. With >99 percent autovalidation, techs can spend their time on the more critical testing performed in the lab," Shirley elaborated.

She continued, pointing out other analyzer features that also need consideration in times of COVID-19:

- High-specificity D-Dimer is critical to assess severity in COVID-19 patients. Using a high specificity D-Dimer reduces false positive patient results, allowing for a better prognostic evaluation with this biomarker.[1]
- Anti-Xa is recommended over APTT for the heparin monitoring of these hypercoagulable patients that may present with elevated levels of fibrinogen and factor VIII.[2]
- On-demand testing of HIT assays is also needed for these hemostatically challenged patients.

Danette Godfrey, Director of IVD Product Marketing at Sysmex America, located in Lincolnshire, IL, added, "The pandemic has stretched and challenged testing personnel and provided new workflows for personnel to adapt to. Automation in analytical laboratory instruments in hematology, urinalysis, flow cytometry and laboratory information solutions continue to improve efficiency and provide time savings for customers. Such improvements are realized through walk-away testing, maintenance, automated rerun/reflex testing and integrated smear preparation and automated smear review. These capabilities improve operational efficiencies, result turnaround times, and overall delivery of patient care. The pairing of these hardware solutions, along with new cloud-based informatics solutions, continue to trend in the industry."

Training protocols amid pandemic

Prior to the beginning of 2020 and the lab industry's introduction to COVID-19, lab directors were able to follow an established protocol when training new employees. This training method was subject to change when the same existing rules and regulations were reviewed to ensure they accommodate the specific training and testing demands of COVID-19 for existing and new lab personnel.

Because of new social distancing practices, Nunez noted that lab directors now rely on multimedia options, such as Zoom and Skype meetings, as well as webinars and remote training sessions, to ensure proper instruction is given to all lab employees.

Simon Shorter, Senior Director, IVD Product Marketing at Sysmex America, disclosed, "Our customers have continued to leverage remote learning and analyzer training, which have remained available during the difficult and restrictive travel circumstances. We have been providing certificates and continuing education units (CEUs) to laboratory technicians across the world with Virtual Instructor Led Training (VILT), e-learning and webinars."

Two areas that still need improvements prior to training are labor and QC issues, according to Shirley. "Today's instruments should be able to detect under-filled tubes and samples that have unacceptable levels of hemolysis, lipemia and/or icterus. Currently this is a labor drain, or process that may be skipped – with the potential of erroneous results being released."

She continued, "The other area prone to problems is the execution of the lab's quality control (QC) policy. With QC material stable up to 24 hours, it may be loaded onto the instrument on first shift. With the auto QC function, the instrument will run QC at the specific time and upon the use of a new vial throughout the day. Should the QC be out, test results will be suppressed until the QC issue is resolved. This is a huge time and labor savings – not only for the tech, but also for the supervisors reviewing QC."

Lab industry challenges

Among many challenges facing manufacturers of analyzers – especially in the era of COVID-19 – one of the top priorities is

to remain flexible and ready for anything that comes along. Whether that is from a large spike in coronavirus cases or a treatment-resistant strain of influenza, the diagnostics industry must remain ready to detect and treat whatever possible next pandemic presents itself in the future.

"The lab industry continues to innovate solutions to combat infection management. The situation lends itself to reliance on the industry's scientific leaders to find the solutions customers need and remain agile to the changing agents of infection. In doing so, the laboratory industry must remain flexible and responsive to the changing needs of the market and consider novel solutions to address the impact of unforeseen supply chain interruptions to ensure minimal impact to day-to-day operations for laboratories and patients," said Godfrey of Sysmex America.

Other challenges on the list included standardization, based on Shirley's comment, "For many vendors, the ability to offer a standardized solution is their challenge," and space in the lab for analyzers to do their job best, according to Nunez, who said, the "space of analyzers to generate results" is what's needed in the lab.

Future analyzers forecast

Looking to the future of the analyzers market and the trends the industry can expect to see, Shirley from Instrumentation Laboratory asserted, "Hemostasis is one of the smaller test volumes of the lab and often upgrading or replacing these instruments is not a priority. With on-demand testing for HIT, this smaller area of the lab has become more important to supporting the hospital goals for improving patient care. Also, with the dwindling supply of qualified techs, having instruments that can implement lab policies is more desirable. It is our opinion that the industry forecast for these solutions will continue to grow."

Nunez from Dynex summarizes a simpler, but more direct, correlation about the future of the analyzers market. He said, "The forecast keeps changing because policies keep changing."

Commenting on the future forecast, Godfrey suggests medical and lab professionals work together for the greater good of both industries.

"The analyzer market continues to be as impacted as the rest of the lab industry with the uncertainty and unpredictability that ensues with the current state of affairs. While the extent of the impact brings ambiguity, the need for clinical laboratory solutions to support medical professionals remains constant," she said.

Regardless of what the future holds for the clinical lab analyzers market, the one thing that remains constant is change. And as changes in disease detection and management keep coming, the lab industry and its analyzers will keep meeting the challenges that the new trends present.

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Emerging techniques in spatially resolved molecular profiling

By John Brunstein, PhD

We're all familiar with ISH (in-situ histochemistry) and FISH (fluorescent in-situ hybridization). Aside from these being common tools – perhaps even better described as essential – for the anatomic pathologist, they can provide visually stunning images. It would be hard to imagine a challenger for title of "most common journal or book cover image type" other than multicolor confocal microscopy images. The beauty of these is purely a bonus on top of the utility in both diagnostic and research applications to visualize spatially resolved cellular components. In this edition of The Primer, we're going to look at some emerging new methods for generating this type of data.

These types of images can be generated by localization of particular antigens, such as proteins or complex sugars, representing the end products of expression of genetic pathways, or they can directly target nucleic acid elements. Since in most normal cells of an organism the DNA content is identical, targeting DNA is generally going to lead to some pretty boring, uninformative, monochrome images.

Exceptions to this are, of course, where explicit DNA variations are being probed, such as known chromosomal translocations (a common target of FISH) or to localize cellular or even subcellular occurrence of a pathogen. What's more likely to be of variation and interest, however, is RNA, where expression is going to be different from cell to cell, based not only on the cell type but also a complex set of cell signalling pathways that regulate gene expression (RNA transcription). Let's consider each of these approaches – antigen- and nucleic acid-based – in turn, highlighting for each what some of the limitations of common current methods are, and what some new techniques might be to address these shortcomings.

Antigen-based approaches – traditional methods

Antigen-based methods most commonly rely on using specific antibodies to tag the target(s) of interest. The chemistry part of ISH comes about when these antibodies are linked (usually indirectly, via a secondary antibody, for reasons of reagent supply-chain simplicity) to an enzyme, which, in turn, catalyzes the localized deposition of a stain at the site(s) of antibody binding. Stains are generally monochrome in nature, meaning a single target can be visualized per image.

Alternatively, the secondary antibody can be fluorescently labeled, which opens this up a bit by allowing for the possibility of simultaneously and separately distinguishing up to about four different targets per image. More than that generally isn't feasible just due to the physics of fluorophores, which tend to have fairly broad excitation and emission spectra. Maintaining differentiable signals requires spacing these – at least the emissions side – out across the visible spectrum, and then using dedicated filter sets to observe them independently before recombining into that image destined for the next journal cover. This places practical limitations on the number of colors (targets) per image.

Emerging antigen-based approaches

Imagine if there were a method to selectively image antigens (biological macromolecules) that neither required the availability of a suitable antibody, nor was effectively restricted in the number of different targets it could separately label within a single image. What sounds magical not only exists, and it's not even new; mass spectrometry imaging (MSI) data has been showing up in conferences for decades.

Essentially, it works by preparing a thin section much as for ISH, then placing that tissue section on a movable stage within a mass spectrometer. A mass spectral data set is collected from one point on the section, then the stage is moved to allow another, spatially separated data set to be obtained. (There are two different methods of achieving this, microprobe or ion microscope based, but for purposes of our overview the net results are similar). Within each mass spec data set, characteristic ion masses are used to indicate the presence and relative abundance of targets of interest.

Very large numbers of targets can be separately classified in this manner, with each target artificially color-coded onto a spatial image where each data set is represented at its location within the sample. A further benefit of this approach is that the data can be retroactively queried for additional targets of interest – if it's something with a characteristic M/Z (mass over charge) ratio, you can look in old data sets for it and its distribution.

At this point, the most obvious question is, "why isn't this more widely used?" The answer almost certainly is because the instrumentation required is very expensive (particularly when contrasted against routine IHC). It can also suffer from poor spatial resolution in comparison to more traditional methods. Although complexities exist in that different MSI approaches have different resolution capacity, the one of most interest here for suitability to lipid and polypeptide targets, MALDI-(Matrix Assisted Laser Desorption Ionization) based MSI, has around 20 µm resolution.

It's also rather slow in comparison to direct visual imaging of IHC and has larger data storage and processing requirements. It's not inconceivable that future iterations of the technology could become less costly and become more widely adopted. For now, it's an incredible technical solution available in a limited number of labs in search of a compelling use-case scenario.

Meanwhile, back in the nucleic acids…

On the nucleic acid side, we considered above that most applications would involve RNA targets. "Spatially resolved transcriptomics," as it is sometimes referred to, has been done in a large number of different ways, which range

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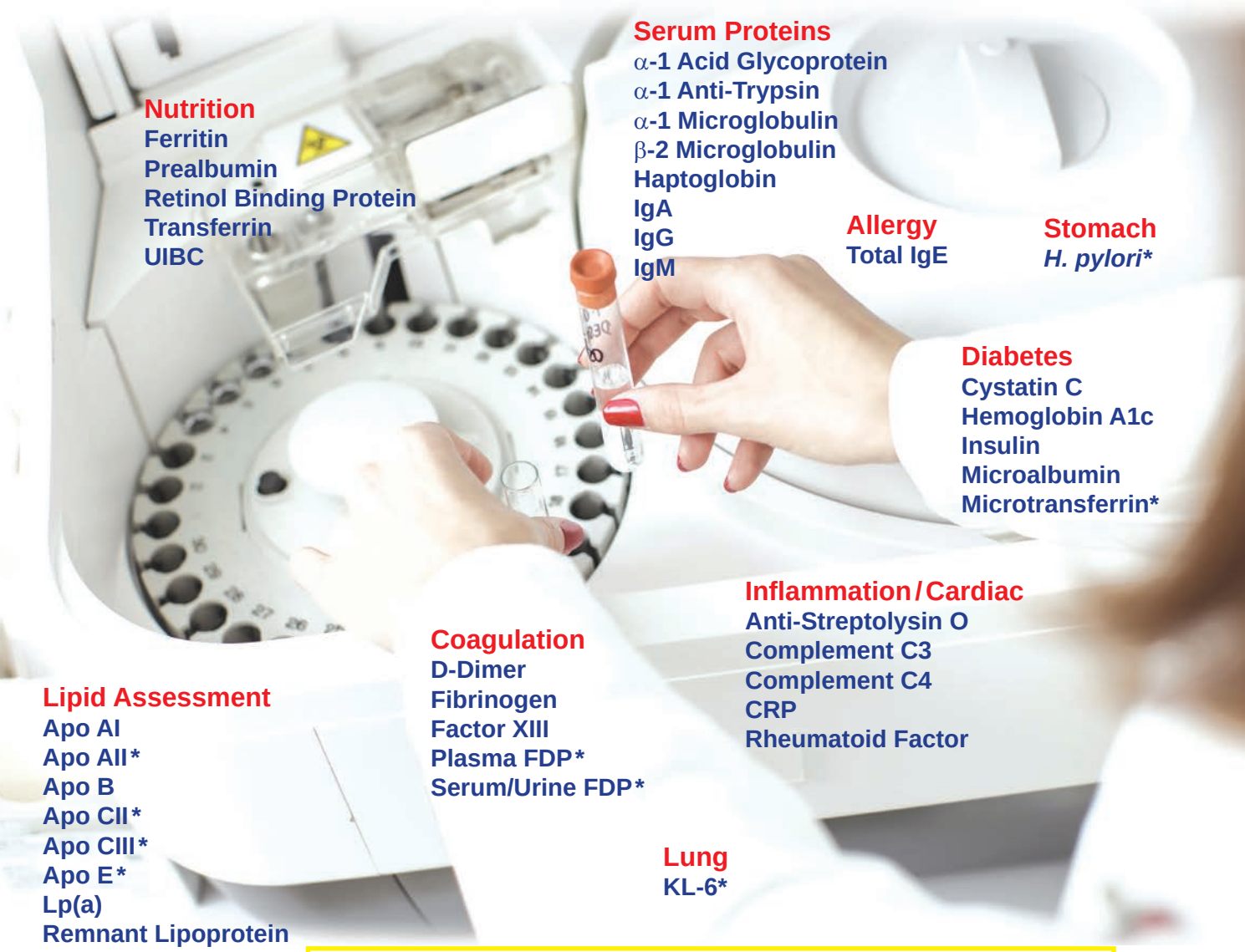

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in the number of targets that can be analyzed and the physical size of the region tested; in general, there is a trade-off between these two (for an interesting graphic presentation of this, readers are directed to reference 1 below).

One generic path to molecular in situ analysis is through the use of laser capture microdissection (LCM) to visually select and isolate single cells or groups of cells from within a tissue section for nucleic acid extraction. Once this is done, any and all molecular tests can be run on this template, up to and including whole genome sequencing (or more likely, whole exome/transcriptome sequencing). While potentially providing great depth of information, this approach doesn't lead to nice graphic images as it's destructive in nature. It also requires some reason or rationale to select what portions of a tissue section are captured for further analysis; likely requiring some prior, more traditional staining method such as IHC already.

At the other extreme of the spatial area versus depth of analysis lie techniques such as in-situ PCR (usually for a single target) or, more commonly now, in-situ hybridization (ISH). Both of these work by nucleic acid base pairing to complimentary sequences (by labeled primers for PCR, and by labeled probe for ISH). The PCR-based approach then requires the addition of enzyme and optimized thermocycling, in return for which high sensitivity is achievable, while ISH trades less sensitivity for simplicity.

Both of these share the visualization modes (and thus inherent challenges) of IHC described above: enzymatic dye deposition is monochrome, and fluorescent methods are usually just a few colors per section. Making in-situ PCR multiplex involves further significant technical challenges, as all targets should amplify under a shared set of thermocycling conditions – a requirement not always easily met. Overall, these methods can provide good spatial resolution (and quantitative data in the case of ISH) for a limited number of targets per tissue section.

Emerging nucleic acid methods

On this side of our topic, some of the emerging approaches involve substituting enzyme-based signal amplification (PCR or tyramide signal amplification) for direct hybridization-based amplification. One variant of this approach is known as Hybridization Chain Reaction. In this method, target-specific probes share regions of complementarity to a complimentary pair of labeled, partially palindromic oligonucleotides (let's call them A and A'). These normally form into self-annealed hairpin structures, but in an isothermal process not requiring any enzymes, natural transient unfolding of one of these (A) allows it to hybridize to a tail portion of the target probe in a manner that blocks refolding while localizing label to probe site.

The exposed unfolded section of (A) then attracts hybridization by its pairing partner (A'), adding more label and driving unfolding and hybridization of another copy of (A), and so on.[2] Publications using this method have shown good sensitivity and specificity with low background signal levels, while allowing for multiplexing within the constraints of fluorescence reporting already noted.

While this space generally sticks to discussions of methods and technologies without reference to specific products or vendors, the above method leads inescapably to mention of not just one, but two specific products. The first, known as RNAscope,3 also employs hybridization amplification, albeit by a different strategy (target-specific nucleic acid probes are bound through tag sequence matches to preamplifier probes, which in turn hybridize multiple amplifier probes and labels, essentially a form of what's called branched chain DNA amplification).

In its fluorescent label incarnation, this method has seen increasingly wide use at least within research publications. An interesting twist on this comes when the fluorescent label is exchanged for a form of more complex, machine-scorable "barcodes." Unlike fluors with limited multiplexing due to spectral overlap, large numbers of these labels remain uniquely differentiable with proper instrumentation. One such platform is from nanoString and pairing of their labeling and imaging approach with RNAscope for the target acquisition is the basis for a product they call the GeoMX Digital Spatial Profiler. Product literature indicates greater than 1,500 RNA target probes are available on this platform, which can simultaneously provide good spatial imaging resolution combined with very high target multiplicities.

Conclusions

Decades of training, experience, and familiarity with traditional IHC (including, critically, a good understanding of its own particular processing artifacts) is not going to be going away any time soon – it's too useful, too cost effective, and too entrenched. An additional hurdle is that application of methods such as those outlined here, particularly on the nucleic acid side, are generally best performed on tissue prepared with "molecular friendly" fixative strategies as opposed to traditional formalin fixation (note use of "best," particularly for short target sequences, hybridization-based approaches, and controlled formalin fixation times; traditional formalin fixed paraffin embedded (FFPE) tissue is amenable to molecular analysis, albeit less than ideal).

The flexibility and multiplexing capacity of these emerging methods on both the antigen and nucleic acid sides are, however, exciting. The images under analysis in the anatomic pathology lab in the not too distant future may well start to be even more dramatic, multicolored, and rich in data than those images gracing today's covers.

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John Brunstein, PhD, serves as an Editorial Advisory Board member for MLO. John is also President and CEO for British Columbia-based **PathoID, Inc.**, which provides consulting for development and validation of molecular assays.

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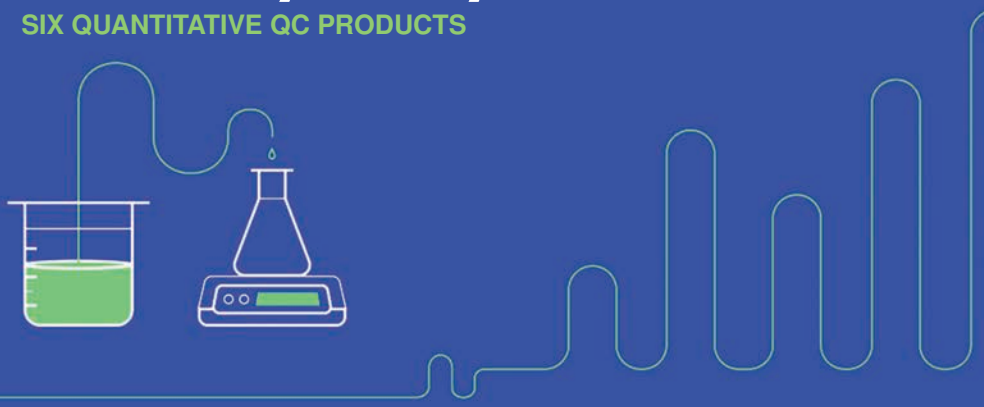

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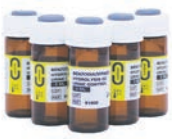

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Transfusion medicine at Moffitt Cancer Center focuses on best practices

By Linda Wilson

Transfusion medicine is an important part of the treatment process for many cancer patients, whose disease and treatment might lead to bleeding or clotting issues, too few red blood cells, or other hematologic issues.

To learn about new developments in this field, *Medical Laboratory Observer* interviewed Kaaron Benson, MD, Medical Director of the Blood Bank and Chemistry Lab at Moffitt Cancer Center in Tampa, FL, a Comprehensive Cancer Center as designated by the National Cancer Institute. Benson, a pathologist, focuses on issues such as the mitigation of adverse events and on human leukocyte antigen (HLA) typing in support of allogeneic blood and marrow transplantation (BMT). She also directs the extracorporeal photopheresis program – a procedure in which white blood cells (WBC) are treated with a photosensitizing drug and exposed to ultraviolet light.

Kaaron Benson, MD
Courtesy of Moffitt Cancer Center

Benson, who has been at Moffitt since 1989, completed a fellowhship earlier in her career at the American Red Cross Blood Services in Los Angeles, where she also served as Assistant Medical Director.

Since it opened its doors in 1986, Moffitt Cancer Center has treated patients from every state and many countries.

When is a red blood cell (RBC) transfusion clinically indicated for cancer patients?

Our indications for cancer patients are similar to other patient populations in that we transfuse for hemodynamically unstable, acutely bleeding patients; transfuse for symptomatic anemia with hemoglobin <8 g/dL; transfuse for acute myocardial ischemia with hemoglobin <9 g/dL; and will consider transfusion in asymptomatic patients who have hemoglobin <7 g/dL, although it may be unnecessary in a stable patient, especially those with chronic anemia.

We ask that single-unit RBC transfusion is considered first, in contrast to the outdated double-unit transfusion minimum of the past. We do use a transfusion threshold of <9 g/dL for patients prior to photopheresis or peripheral blood stem cell collection and higher thresholds may also be used for patients with unique needs such as in sickle cell anemia patients with prior stroke.

Approximately what percentage of Moffitt's transfusions are with RBC units?

In 2019, we transfused 15,699 RBC units and performed 11,621 platelet transfusions, so you can see that 57 percent of our cellular components transfused are RBCs and 43 percent are platelets. Another way to look at it is that 1.4 RBC units are transfused for every platelet transfusion.

When it comes to transfusion medicine in oncology, what are some new developments in the science of RBC transfusions that are being incorporated into best practices at Moffitt?

Many have adopted the phrase "less is more" as we now have several studies showing that restrictive transfusion practices using lower hemoglobin thresholds may work as well or better than more liberal transfusion practices using higher thresholds. We have also found that for many patients, we do not have to transfuse the traditional two units of RBCs, and that many otherwise stable patients may do quite well with single units of blood when there is an indication for RBC transfusion.

Why does Moffitt routinely use irradiated blood in its transfusions?

Irradiated cellular blood components (RBCs and platelets) are routinely provided to our oncology patients since many patients have a clear need due to risks for transfusion-associated graft-versus-host disease (GVHD), such as recipients of blood and marrow transplantation or patients with hematologic malignancies. As we have an irradiator onsite, we have found it best to have an inventory of irradiated cellular components that are readily available should any of our patients in need require these components quickly. While other patient diagnoses may be at less risk for transfusion-associated GVHD, we have decided to err on the side of caution and transfuse these irradiated components to our oncology population.

When are plasma transfusions medically indicated in cancer care?

Some prime examples are patients with thrombotic thrombocytopenic purpura (TTP) who require fresh frozen plasma (FFP) for their therapy that includes plasma exchange. Some of our patients may have coagulation factor depletion during severe infections, disseminated intravascular coagulation (DIC), or bleeding and may require plasma transfusions at that time.

When are platelet transfusions medically indicated in cancer care?

Oncology patients often have low platelet counts due to their disease preventing them from making sufficient quantities of their own platelets, or due to our therapies like chemotherapy, or BMT, which can cause a temporary suppression of the patient's platelet production. Also, patients with active bleeding can deplete their platelets and may require platelet transfusion along with the RBCs and plasma, which are typically needed in hemorrhaging patients.

What are new developments in the use of plasma and platelet transfusions in cancer care?

With the current COVID-19 pandemic, we are using COVID-19 convalescent plasma (CCP) for our oncology patients who test positive for SARS-CoV-2 RNA. We have also begun to

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

use pathogen-reduction technology (PRT)-platelets when we can obtain these components, so that the risk of transfusion-transmitted infection is reduced. Bacterially contaminated platelets remain the greatest risk for serious transfusion-associated infection. Moffitt has also seen a rare adverse event from platelets, i.e., hemolysis of patient RBCs due to donor plasma during platelet transfusion.

Fortunately, the three patients that had this low-risk event in Moffitt's 30-plus years of operation did all fully recover but all occurred in smaller-sized patients who were non-group O receiving group O platelet transfusion. Based on these cases, we established a new mitigation step of plasma volume reduction of group O platelets to be transfused to smaller (less than 60 kg) non-group O recipients.

Will you explain the science behind Intercept-screened platelets and why some cancer centers choose to use these platelets for transfusions? Does Moffitt use these types of platelets?

Intercept platelets are apheresis platelets exposed to the psoralen amotosalen, which will bind to any nucleic acids present in the sample. Upon exposure to UVA light, crosslinking of the nucleic acids occurs, thus, preventing pathogen replication. The Intercept method has been shown to inactivate a broad range of pathogens, most importantly bacteria but also viruses, parasites, spirochetes and leukocytes. As bacterially contaminated platelets remain one of our chief concerns due to the high morbidity and potential mortality of these events, we have been eager to use PRT platelets and are slowly ramping up our inventory of this preferred component.

What advancements are on the on the horizon for reducing pathogens in blood products?

Currently here in the United States, we have pathogen reduction technology (PRT) platelets but do not yet have PRT RBCs. Methods for PRT RBCs have been developed and clinical trials have begun. With the PRT method, we may be able to ultimately discontinue some of the donor testing that we currently employ. We may be able to allow deferred donors to return to blood donation and possibly relax some of our donor restrictions.

What other steps can pathologists take to reduce the risk of adverse events associated with transfusions?

We can educate our medical colleagues to use evidence-based medicine when transfusing patients, educate our nursing colleagues to ensure proper patient- and blood-component identification at the time of transfusion, encourage patients' loved ones to consider blood donation to replenish this limited resource, and serve as a ready source of guidance when questions arise.

Has Moffitt noted shortages in the supply of blood products as a result of the pandemic and people's reluctance to donate blood?

Fortunately, our new blood suppliers – LifeSouth Community Blood Centers and SunCoast Blood Centers – have done an excellent job of keeping an adequate supply of blood on our shelves. In the past, we have experienced some shortages, generally over holidays and summer months. We did develop a blood shortage action plan due to the pandemic but, thankfully, have not had to implement it to date.

Moffitt signed agreements with both LifeSouth Community Blood Centers and SunCoast Blood Centers earlier this year. How have these agreements improved Moffitt's access to blood? How had Moffitt been sourcing blood before signing the agreements?

Prior to signing these agreements, we had used OneBlood as our sole blood supplier. OneBlood and the former Florida Blood Services (and their predecessor Southwest Florida Blood Bank) had been our sole supplier since Moffitt first opened its doors back in 1986. We made the transition from a single supplier to a dual system in hopes of ensuring a consistent and adequate supply of blood. We hope that the adage "two are better than one" applies in this case.

Courtesy of Moffitt Cancer Center

Moffitt Cancer Center At-A-Glance

- Opened in 1986 in Tampa, FL
- Licensed Beds: 206
- Annual Hospital Admissions: 9,465
- Annual Outpatient Visits: 450,760
- Annual Surgical Cases: 11,601
- Employees: 6,500
- Active Clinical Trials: 450

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Company Name	Website	Name of Molecular Test	Type of Test	Platform/Application	Time to Results
Access Bio	https://carestart.com/	CareStart COVID-19 MDx	RT-PCR	Common PCR processing systems	83 minutes
Access Genetics	https://www.prnewswire.com/news-releases/fda-issues-eua-for-orarisk-covid-19-rt-pcr-test-from-oraldna-labs-301096815.html	OraRisk COVID-19 Test	RT-PCR	N/A	1-2 days
Acupath Laboratories	https://www.acupath.com/covid-19-testing/	Acupath COVID-19 Real-Time Assay	RT-PCR	Thermo Fisher TaqPath RT-PCR platform	24-48 hours
Alpha Genomix Laboratories	http://alphagenomix.com/	Alpha Genomix TaqPath SARS-CoV-2 Combo Assay	Molecular	Roche MagNA Pure 96 instrument	N/A
BayCare Laboratories	https://baycare.org/coronavirus#.X1pvwHIKiCo?hcmacid=a0Z1a0000046RCJEA2	BayCare SARS-CoV-2 Assay	RT-PCR	N/A	48-72 hours
BillionToOne	https://billiontoone.com/covid-19/	https://baycare.org/coronavirus#.X1pvwHIKiCo?hcmacid=a0Z1a0000046RCJEA2	Molecular	N/A	N/A
Biomeme	https://biomeme.com/	Biomeme SARS-CoV-2 Real-Time Test	RT-PCR	Franklin PCR Instrument Bio-Rad CFX96 Applied Scientific QuantStudio RT-PCR systems Applied Scientific 12X Flex Instrument	N/A
Capstone Healthcare	https://capstonehealthcare.com/covid19-testing/	Genus SARS-CoV-2 Assay	Molecular Assay	Applied Biosystems QuantStudio 12X Flex Instrument	N/A
CENTOGENE US	https://www.centogene.com/covid-19/testing/about-the-sars-cov-2-test.html	CentoFast SARS-CoV-2 Assay	RT-PCR	N/A	72 hours or less
DiaCarta	https://diacarta.com/products/covid19/sars-cov-2	QuantiVirus SARS-CoV-2 Test Kit	Multiplex Test Kit	Thermo Fisher (ABI) QuantStudio 5 Thermo Fisher (ABI) 7500 Fast Dx Bio-Rad CFX 384 Roche Light Cycler 480 II	Less than 2 hours
Diagnostic Solutions Laboratory	https://www.diagnostic-solutionslab.com/tests/covid-19-sars-cov-2	DSL COVID-19 Assay	Molecular	N/A	1-2 days
DxTerity Diagnostics	https://dxterity.com/sars-cov-2-test-covid-19/	DxTerity SARS-CoV-2 Test	RT-PCR	N/A	24-48 hours
Eli Lilly and Company	https://www.fda.gov/media/140543/download	Lilly SARS-CoV-2 Assay	Molecular Assay	Applied Biosystems QuantStudio Real-Time PCR Systems	N/A
Enzo Life Sciences	https://www.enzolife-sciences.com/ENZ-GEN215/ampiprobe-sars-cov-2-assay-kit/	AMPIPROBE SARS-CoV-2 Test System	Molecular	Enzo GENFLEX Thermo Scientific QS5 RT-PCR instrument	N/A
Fluidigm	https://www.fluidigm.com/singlearticles/covid-19-diagnostics	Advanta Dx SARS-CoV-2 Assay	RT-PCR Assay	N/A	192 samples - under 3 hours
Gene By Gene	https://genebygene.com/news/covid-19-diagnostic-testing/	Gene By Gene SARS-CoV-2 Detection Test	Molecular	N/A	Less than 24 hours
Guardant Health	https://guardanthealth.gcs-web.com/news-releases/news-release-details/guardant-health-receives-fda-emergency-use-authorization-its	Guardant-19	Molecular	N/A	24 hours
Helix	https://helixmdx.com/	Helix COVID-19 Test	Molecular	N/A	Less than 48 hours
Inform Diagnostics	https://www.informdx.com/our-services/covid-19-testing/	Inform Diagnostics SARS-CoV-2 Assay	RT-PCR	ABI 7500 and QuantStudio real-time PCR systems	1-2 days
LumiraDx UK	https://www.lumiradx.com/us-en/what-we-do/diagnostics/fast-lab-solutions/rna-star	LumiraDx SARS-CoV-2 RNA STAR	Molecular	N/A	12 minutes
MiraDx	https://miradx.com/covid-19-testing/	MiraDx SARS-CoV-2 Assay	RT-PCR	N/A	24-48 hours
PreciGenome	https://www.precigenome.com/coronavirus-covid19-pcr-assay	FastPlex Triplex SARS-CoV-2 Detection Kit	RT-Digital PCR	ABI 7500 and Bio-Rad CFX96 PCR systems	N/A

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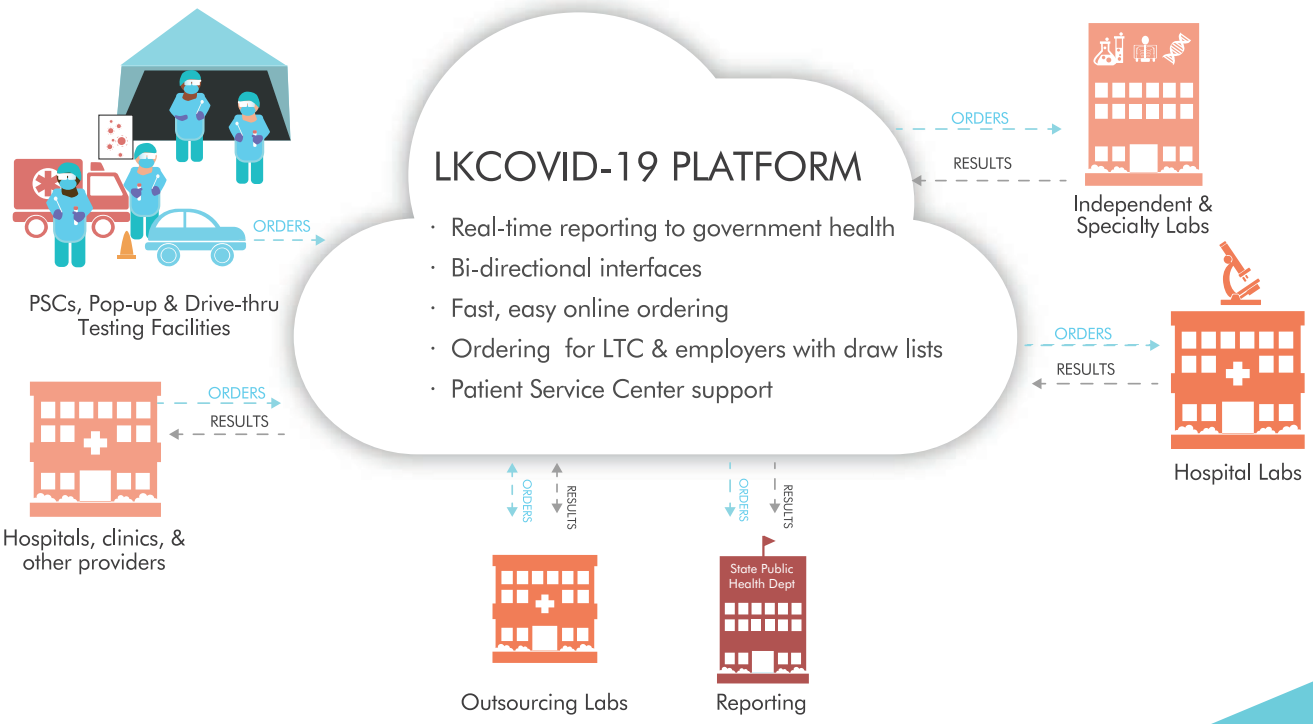

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Company Name	Website	Name of Molecular Test	Type of Test	Platform/Application	Time to Results
Psomagen	https://psomagen.com/covid-test/	Psoma COVID-19 Test	RT-PCR	Roche LightCycler 480 instrument	N/A
Roche Molecular Systems	https://www.roche.com/media/releases/med-cor-2020-09-04.htm	cobas SARS-CoV-2 & Influenza A/B	Molecular, Multi-Analyte	cobas 6800 and cobas 8800	96 samples in 3 hours
Solaris Diagnostics	https://solarisdx.com/coronavirus-2019/	Solaris Multiplex SARS-CoV-2 Assay	Molecular	Applied Biosystems QuantStudio 5	N/A
T2 Biosystems	https://www.t2biosystems.com/products-technology/t2sars-cov-2-panel/	T2 SARS-CoV-2 Panel	Molecular	T2Dx Instrument	Less than 2 hours
Trax Management Services	https://gotraxconnects.com/testing-solutions	PhoenixDx SARS-CoV-2 Multiplex	Molecular	N/A	6-8 hours
Wren Laboratories	https://www.wrenlaboratories.com/covid-19/covid-19-testing	Wren Laboratories COVID-19 PCR Test	RT-PCR	QuantStudio 7	N/A

COVID-19 SEROLOGY TEST UPDATES

Company Name	Website	Name of Serology Test	Type of Test	Platform/Application	Time to Results
Access Bio	https://www.apacor.com/products/carestart-covid-19-igm-igg/	CareStart COVID-19 IgM/IgG	Serology IgM and IgG, Lateral Flow	N/A	10 minutes
Beckman Coulter	https://www.beckman-coulter.com/products/immunoassay/access-sars-cov-2-igg-antibody-test#/specifications	Access SARS-CoV-2 IgG	Serology IgG, CLIA	Dxl 800	25 minutes
Biocan Diagnostics	https://www.rapidtest.ca/covid-19	Tell Me Fast Novel Coronavirus (COVID-19) IgG/IgM Antibody Test	Serology IgM and IgG, Lateral Flow	N/A	10-15 minutes
BioCheck	http://www.biocheckinc.com/NR	BioCheck SARS-CoV-2 IgG and IgM Combo Test	Serology IgM and IgG, CLIA	MS-Fast system	30 minutes
bioMerieux	https://www.biomerieux-diagnostics.com/vidas-sars-cov-2	VIDAS SARS-CoV-2 IgM	Serology IgM, ELFA	All VIDAS Instruments	Less than 30 minutes
bioMerieux	https://www.biomerieux-diagnostics.com/vidas-sars-cov-2	VIDAS SARS-CoV-2 IgG	Serology IgM, ELFA	All VIDAS Instruments	Less than 30 minutes
Diazyme Laboratories	https://www.diazyme.com/covid-19-antibody-tests/dz-lite-sars-cov-2-igg-clia-kit	Diazyme DZ-Lite SARS-CoV-2 IgG CLIA Kit	Serology IgG, CLIA	DZ-Lite 3000 Plus Chemiluminescence Analyzer	N/A
Diazyme Laboratories	https://www.diazyme.com/covid-19-antibody-tests/dz-lite-sars-cov-2-igm-clia-kit	Diazyme DZ-Lite SARS-CoV-2 IgM CLIA Kit	Serology IgM, CLIA	DZ-Lite 3000 Plus Chemiluminescence Analyzer	N/A
InBios International	https://inbios.com/scov-2-detect-igm-elisa-kit/	SCoV-2 Detect IgM ELISA	Serology IgM, ELISA	N/A	2.5 hours
Luminex	https://www.luminexcorp.com/xmap-sars-cov-2-antibody-testing/#overview	xMAP SARS-CoV-2 Multi-Antigen IgG Assay	Serology IgG, FMIA	MAGPIX, Luminex 200 and FLEXMAP 3D	96 samples in less than 3 hours
Megna Health	https://www.megnahealth.com/products/	Rapid COVID-19 IgM/IgG Combo Test Kit	Serology IgM and IgG, Lateral Flow	N/A	15 minutes
Salofa	https://www.salofa.com/en/covid-19-rapid-diagnostic-test-available	Sienna-Clarity COVIBLOCK COVID-19 IgG/IgM Rapid Test Cassette	Serology IgM and IgG, Lateral Flow	N/A	10 minutes
Siemens Healthineers	https://www.siemens-healthineers.com/en-us/laboratory-diagnostics/assays-by-diseases-conditions/infectious-disease-assays/cov2g-assay	ADVIA Centaur SARS-CoV-2 IgG	IgG, Semi-quantitative	Atellica IM Analyzer	25 minutes
Siemens Healthineers	https://www.siemens-healthineers.com/en-us/laboratory-diagnostics/assays-by-diseases-conditions/infectious-disease-assays/cov2g-assay	Atellica IM SARS-CoV-2 IgG	IgG, Semi-quantitative	Atellica IM Analyzer	25 minutes
TBG Biotechnology	http://www.tbgbio.com/en/product/product_detail/52	TBG SARS-CoV-2 IgG/IgM Rapid Test Kit	Serology IgM and IgG, Lateral Flow	N/A	15 minutes

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Choosing the right antibody for successful immunohistochemistry

By Hartmut Pohl

Immunohistochemistry (IHC) is a widely used technique to analyze the anatomy of a tissue of interest and to visualize the expression, localization, and intensity of a specific antigen. Although IHC is a well-established laboratory method with a long-standing history, there is a wide range of factors influencing its outcome. The quality of the staining may be influenced by several variables that need to be considered to produce reliable and consistent results, for instance, antibody selection.

Antibodies are indispensable for laboratories and represent an invaluable tool with multiple applications. Yet, antibodies are also at the nexus of reproducibility issues plaguing laboratories.[1] While maybe not the leading cause, antibodies, and reagents as a whole, are a common source of error and inaccuracy fueling the reproducibility crisis. It is, therefore, crucial to choose the right antibody from the start. For rare targets, it might be difficult to find an antibody at all, while for widely studied proteins, there might be thousands of antibodies to choose from.

With an estimated total of 4.5 million commercial antibodies from 350-plus suppliers available, it can be a daunting task to choose an antibody. However, time spent researching the best product to buy can save time and resources down the line and substantially reduce frustration. In this article, we offer guidance on how to select the right antibody according to the multiple variables.

Define your protein target of interest

Protein targets can be highly complex. For any given protein, a variety of names, abbreviations, isoforms, splice variants and *in vivo* modifications might exist, and sequence identity or homology with closely related proteins pose additional challenges in the form of potential cross-reactivity. Furthermore, cellular binding partners might mask the antibody's binding site. To add to the confusion, sometimes the commonly used names for a given protein target vary across science fields.

As such, make sure that you understand the biology of your protein target and the capabilities of any antibody in question to detect your target under the chosen conditions. Use genetic and protein databases, such as UniProt or GeneCards, to study your target and obtain unique identifiers. If your research depends on the antibody recognizing a specific portion of your target, make sure that the epitope the antibody was raised against is known and within the required domain.

Ensure the antibody suits your sample

Targets vary in their sequence and structure from species to species. Unless the datasheet specifies that the antibody has been validated for a species, there is no guarantee the antibody will work. Therefore, it is recommended that you use antibodies that have been validated specifically for your species of interest. For the commonly used species, specific antibodies are generally available.

However, if you are using exotic species, you might be out of luck more often than not. But despair not. Often antibodies are raised against relatively preserved domains within target proteins, and even if sequence homology of the epitopes is as low as 75 percent, there is a decent chance that the antibody might recognize your target. In these instances, it is important to validate the antibody's performance and specificity for the given species.

Choose a compatible antibody

It would be ill-advised to assume that an antibody that has been shown to detect a target in one application will do so under other circumstances. A given antigen might, for example, require that the target protein is present in its native, folded form or might only be accessible in a denaturated protein. Thus, antibodies that work in Western blot with denaturated proteins might not work in immunofluorescence of frozen sections where antigens are present in their naïve conformation – and vice versa. Certain fixation methods might compromise an antigen, or permeabilization or dissociation steps might be required to make an antigen accessible for an antibody. For example, an antibody detecting a membrane target in immunocytochemistry might not work in flow cytometry, simply because the target antigen is not on the cell's surface.

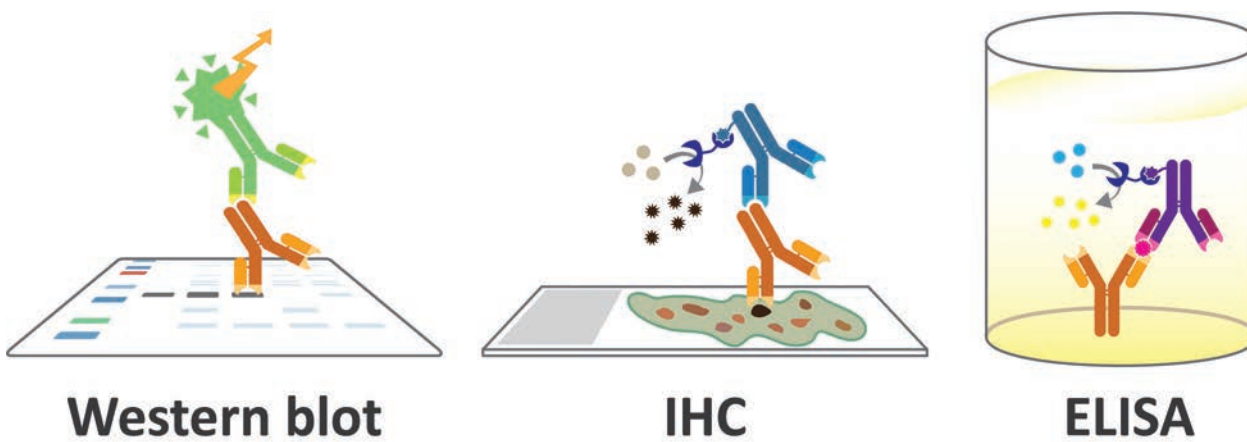

Figure 1: Common applications for antibodies.

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

It is often preferable to buy a couple of antibodies with proven, outstanding performances for specific applications over a single antibody that supposedly does it all without any proof that backs up this claim.

Carefully select host species

There's good reason that a variety of antibody species, types and clonalities exist – they all offer different advantages and pitfalls. When choosing a host species, it might be worth it to have a look at available secondary antibodies, as well as potential combinations for multiplexing. It is recommended to avoid antibody host species that are identical with the species of your target samples to avoid interference with immunoglobulins present in the sample – although workarounds do exist. Furthermore, the usage of different types of immunoglobulins (IgG, IgM, IgE etc.) might offer advantages in cross-reactivity and multiplexing.

Understand how clonality can affect results

Monoclonal antibodies are produced by hybridoma cell lines, immortalized, cloned B-cells from immunized animals that are all genetically identical and, therefore, generate only one specific antibody of a fixed sequence and structure. Common host animal species include rabbit and mouse. The resulting antibodies display greater specificity towards one particular antigen epitope. Hybridoma cell lines may provide less variation in reactivity between different lot productions.

An advantage of using monoclonal antibodies is the greater likelihood of reproducing results as a consequence of less variation between different lot productions. Greater mono-specificity also provides decreased reactivity with other antigens, resulting in reduced background staining. However, a natural consequence of this mono-specificity is a less robust sample signal compared to polyclonal antibodies. Protocols that result in subtle shifts in epitope structure can potentially have drastic effects on staining.

Choose a compatible antibody

It would be ill-advised to assume that an antibody that has been shown to detect a target in one application will do so under other circumstances. A given antigen might, for example, require that the target protein is present in its native, folded form or might only be accessible in a denaturated protein. Thus, antibodies that work in Western blot with denaturated proteins might not work in immunofluorescence of frozen sections where antigens are present in their naïve conformation – and vice versa. Certain fixation methods might compromise an antigen, or permeabilization or dissociation steps might be required to make an antigen accessible for an antibody. For example, an antibody detecting a membrane target in immunocytochemistry might not work in flow cytometry, simply because the target antigen is not on the cell's surface.

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Polyclonal antibodies in contrast are extracted directly from the blood of the host animal, and not from cultured B-cells. As multiple different B-cell clones become activated, the resulting polyclonal antibodies are a mix of antibodies of different structure and binding affinities and specificities, including off-target antibodies. Downstream purification steps can increase the specificity of a polyclonal antibody mix (see below). The advantage is that antibody production is streamlined, and a wider variety of host species can be used, as the immortalization and culturing of B-cells can be omitted. These host species include horse, donkey, pig, mouse, and rabbit, but also less-common animals – from chicken and guinea pig to camel.

Due to polyclonal antisera – including multiple antibodies from multiple B-cell clones – there is a greater potential to recognize differing epitope configurations. Subsequently, this also means that one should expect greater variation between different lot productions. An inherent advantage of using polyclonal antibodies is greater signal detection due to the multiple epitope configurations that can be recognized. There is also a greater tolerance for changes in experimental conditions that could possibly induce changes to epitope structure. However, greater epitope recognition may also result in more non-specific staining that results in higher background signal. Polyclonal antibodies may show lower chances of reproducing experimental results as a consequence of greater lot-to-lot variation.

Check formulation and purification

Antibodies come in a variety of formulations and various degrees of purification. The simplest presentations are probably neat serum, ascites fluid or cell culture supernatant. While they are easily produced, readily available and often of low cost, their content, consisting of other immunoglobulins and proteins might be detrimental and purified antibody products are generally preferred. Polyclonal antibodies require more thorough purification. Due to their production methods, monoclonal or recombinant antibodies are of higher purity, but even those may, without purification steps, contain unwanted immunoglobulins, if the cell cultures contained undefined serum.

Antibodies might be purified by a variety of methods. The simplest method is some form of physiochemical fractionation to isolate a protein fraction that is highly enriched in immunoglobulins but may contain other proteins. The most common is probably a purification step for immunoglobulins, regardless of their specificity, such as using the specific binding of protein

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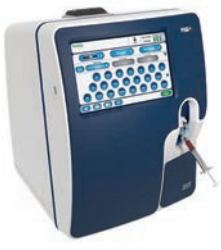

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A to immunoglobulins. The gold standard is affinity-purified antibodies that have been selectively purified for their ability to bind the target antigen.

Look for (independent) validation

An antibody should ideally be validated by the supplier for at least your protein target, species and general application type, but it is impossible for any supplier to validate all conceivable applications and protocols. Literature references are a great source of validation. Finding the right antibody can be difficult and costly. Suppliers may offer solutions should you want to challenge an antibody with new applications or end up with unsatisfactory results.

Consider detection method and system

All immune-mediated techniques rely on the means to detect the antibody that was used to detect and identify the protein target of interest. A variety of detection methods and systems are available but should be carefully chosen. The most commonly used is indirect detection with conjugated secondary antibodies. Here, a polyclonal antibody that reacts with immunoglobulins of the host species of the primary antibody is used for detection.

The secondary antibody is covalently conjugated with molecular means of detection. These might be fluorochromes for fluorimetric detection, enzymes that can be used to catalyze chromogenic or luminescent reactions, or molecular binding moieties, such as biotin for subsequent binding with (strept-) avidin-based detection reagents. The complexity of detection systems is basically limitless. Exotic conjugates include gold particles for electron microscopy or radioisotopes.

But indirect detection, while often drastically increasing sensitivity and allowing a significant degree of flexibility, might not be suited for all applications. Sometimes a direct link might be preferred, for example, in flow cytometry or immunoprecipitation. Flow cytometry relies on fluorescently labeled primary antibodies, which often limits the selection of suitable antibodies considerably.

Technical support and return policy can save the day

After you have run into severe experimental challenges, a good technical service might be invaluable. The supplier's experts might also be able to assist you should you face difficulties deciding which antibody to buy or whether a given antibody might suit your needs. Do not hesitate to contact the supplier's tech support before buying an antibody. This is a way to not only get invaluable help and insight but also to separate the wheat from the chaff of suppliers.

Be prepared to validate on your own

Even the best-characterized antibody that is beloved by the scientific literature and has enriched many publications is not guaranteed to perform in all settings flawlessly. You limit your resources severely if you only consider antibodies validated exactly for your needs. You should always plan to validate an antibody on your own to some extent. Include the appropriate controls in your experiment to analyze the specificity of an antibody in your precise circumstances.

A useful guide for very thorough antibody validation has been compiled by Bordeaux and colleagues.[2] An increasing number of journals not only require detailed information on the antibodies used in a study (such as name, clone, supplier, catalog and even lot number) but also encourage proof of validation. It is in the interest of us all that scientific data generated with the help of antibodies is reliable and reproducible, but ultimately it is the user's responsibility to use proven experimental tools.

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1. Baker, M. Reproducibility crisis: Blame it on the antibodies. *Nature*. 2015; 521, 274–276.

2. Bordeaux, J. et al. Antibody validation. *Biotechniques*. 2010; 48(3), 197–209.

Hartmut Pohl is an Application Scientist with **Enzo Life Sciences**. He is a Cellular Neurobiologist and previously worked on the cellular mechanisms of demyelination in leading research groups at the ETH Zurich, Switzerland; Cambridge University, UK; and the Centre for Multiple Sclerosis, Barcelona, Spain.

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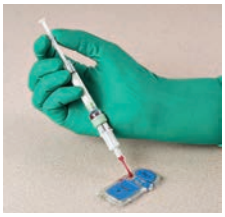

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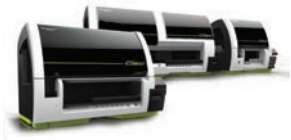

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LABORATORY INNOVATOR

Passion for innovation drives approach to HIT

By Linda Wilson

Marc Probst, MBA, is the chief information officer (CIO) for **ELLKAY**. Prior to joining ELLKAY, he was the vice president and CIO at Intermountain Healthcare in Salt Lake City, Utah. In 2020, Probst was named the CIO of the Year by HIMSS and the College of Healthcare Information Management Executives (CHIME).

You spent nearly 17 years as CIO at Intermountain Healthcare before retiring from that position. After so many years working in a provider environment, why did you decide to join ELLKAY as its CIO?
I worked with ELLKAY as both a customer of the organization and as an adviser. I believe ELLKAY is in a space where there is an incredible need in our industry, and I have a passion around integration as well as a passion around innovation. I recognized that shared passion in ELLKAY and saw the potential to do even more than they are doing today.

Looking back to Intermountain Healthcare, what achievement are you most proud of and why?
It is not even a technology achievement. The thing I am most proud of is the management team that I built. I was so blessed to have a team – a broader team – that I could choose my leadership team from. I am very proud that it was the most diverse team that Intermountain has ever had. They brought incredible insights and background – whether it was technical, clinical, process, or administration. The diversity of this team brought a richness that improved our work and, frankly, me as a person.

The lack of interoperability among disparate health information systems has stymied clinical data analysis and decision support for many years. Do you expect interoperability to improve among these systems, including LIS systems? How will this happen?
I do think it can be improved. I was on the HIT Policy Committee (which provided recommendations to the National Coordinator for Health Information Technology on the meaningful use program for adoption of electronic medical records [EMRs]) for seven years.

During the last two years, we started to deal with interoperability and standards. Since that time, I think we have seen dramatic improvements. I have been a very big advocate for the role that the federal government needs to play to get to true interoperability and standards. It has taken a long time to get started on the curve. But once we are really on that curve, I think we will see a lot of improvement and more interoperable solutions.

How will increased data sharing between electronic health records (EHRs) and LIS impact the day-to-day work at laboratories?
On the lab side, there is huge consumption of data, and often the data that arrives at the lab is not completely accurate or complete. This missing or inaccurate data in the orders must be chased if the lab wants the claim to be processed, costing large amounts of staff time. They have got to receive orders in a way that missing or inaccurate data can be addressed on the front end, right when the order is placed. Then once results are ready to be provided, the line of communication is already clean.

The more standard we get and the more interoperable we get, the quicker things can happen within the labs. It is also going to allow for more comparative data within the industry about what is happening in the lab. One of the real benefits or goals that we should have with interoperability is the real sharing of knowledge – not just data that is in a standard format. It is the ability to take analytics and apply it to that data to give knowledge to the people who are receiving it.

Turning to COVID-19 testing and surveillance, what steps do you think need to be taken to develop a national, electronic system of reporting and aggregating information to monitor disease outbreaks?
We are getting some interesting new technologies around contact tracing (mobile apps that submit data about SARS-CoV-2 infections), and I think they are going to be important. The challenge is, in our society, people have the freedom to opt in or out of how that data gets shared. Another challenge is that the agencies receiving the reports need to be as sophisticated as those sending the reports, or they are not able to decode the data into meaningful results that can be used for the surveillance and detection of outbreaks.

Digital health technology and artificial intelligence will play key roles in our ability to manage a pandemic moving forward. Because there is enough metadata surrounding disease testing, if we can enact interoperability on a larger scale across the industry, I believe we could get really good at identifying what the hotspots are, where the spread from the hotspots is, and how those things relate to each other. With this information and technology, society is empowered to control pandemics or even prevent them from rising to that level of contagion altogether.

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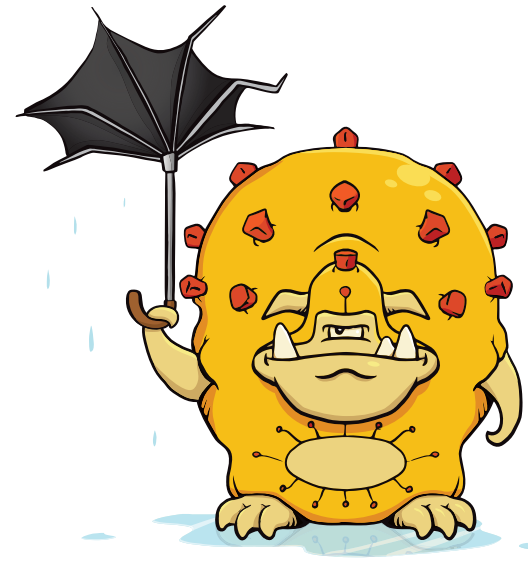

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1 Test. 22 Targets. ~45 Minutes.

Nasopharyngeal Swab in Transport Media: overall 97.1% sensitivity and 99.3% specificity (prospective specimens)[2]
SARS-CoV-2 98.0% sensitivity and 100% specificity (archived specimens)[3]
SARS-CoV-2 100% PPA and 100% NPA (contrived specimens)[4]

The BioFire RP2.1 Panel is a front-line test for labs to help clinicians quickly diagnose and treat upper and lower respiratory infections.

BioFire PN Panel

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1. This test has not been FDA cleared or approved. This test has been authorized by FDA under an EUA for use by authorized laboratories. This test has been authorized only for the detection and differentiation of nucleic acid of SARS-CoV-2 from multiple respiratory viral and bacterial organisms. This test is only authorized for the duration of the declaration that circumstances exist justifying the authorization of emergency use of in vitro diagnostic tests for detection and/or diagnosis of COVID-19 under Section 564(b)(1) of the Act, 21 U.S.C. § 360bbb-3(b)(1), unless the authorization is terminated or revoked sooner. 2. Based on the prospective portion of the clinical study for the BioFire FilmArray Respiratory 2 (RP2) Panel. 3. Based on the archived specimen study in the BioFire Respiratory 2.1 (RP2.1) Panel EUA submission. 4. Based on the contrived specimen study in the BioFire Respiratory 2.1 (RP2.1) Panel EUA submission. 5. The stated performance is the aggregate of the prospective data from the clinical study for the BioFire® Filmarray® Pneumonia (PN) Panel.

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