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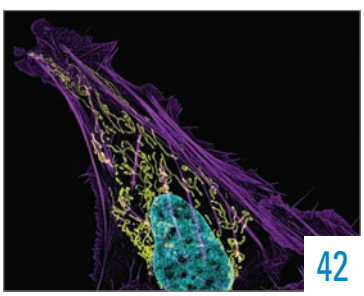
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The SARS-CoV-2 Mu variant emerges

By Linda Wilson
Senior Editor

While Delta is the dominant SARS-CoV-2 variant, a newcomer, Mu, has gained the world's attention.

Mu became the World Health Organization's (WHO) fifth variant of interest (VOI) on August 30. Other variants in this category are Eta (B.1.525), Iota (B.1.526), Kappa (B.1.617.1) and Lambda (C.37).

WHO also has recognized four variants of concern (VOC), a more severe category that includes Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1) and Delta (B.1.617.2).

However, the available information on the Mu variant, or B.1.621, is preliminary and inconclusive.

It was first identified in Columbia in January 2021. Since then, "there have been a few sporadic reports of cases of the Mu variant and some larger outbreaks have been reported from other countries in South America and in Europe," the WHO wrote recently in its COVID-19 Weekly Epidemiological Update.

As of early September, the United States reported 2,462 cases overall, including 60 in the previous four weeks. On the same date, case counts were 1,041 in Columbia, 516 in Spain, 375 in Mexico, 182 in Chile, 170 in Ecuador, 128 in Canada, and 62 in the United Kingdom, according to the Global Initiative on Sharing All Influenza Data (GISAID).

Overall, Mu has been detected in 49 countries.

The WHO said it classified Mu as a VOI because preliminary data showed a potential reduction in the neutralization capacity of vaccines and some treatments, such as convalescent plasma. In general, a variant becomes a VOI if it includes genetic changes that affect transmissibility, disease severity, immune escape, diagnostic or therapeutic escape, and if it has caused community transmission or community clusters in multiple countries with increasing prevalence over time.

As of early September, however, the Centers for Disease Control and Prevention (CDC) had not added Mu to its SARS-CoV-2 variant classification system, which includes four variants of concern (Alpha, Beta, Delta, Gamma) and four variants of interest (Eta, Iota, Kappa and Pango Lineage B.1.617.3).

At a recent news briefing, Anthony Fauci, MD, Director of the National Institute of Allergy and Infectious Diseases and Chief Medical Advisor on COVID-19 to the President, said the United States is keeping an eye on Mu, even though the variant "is not at all even close to being dominant." At this point, Delta accounts for more than 99% of cases, Fauci explained.

Fauci also addressed concerns about whether Mu can evade antibodies, noting that most of the information about the variant so far is preliminary data from in vitro laboratory testing — not clinical data from patients' medical histories. "Not to downplay it; we take it very seriously," he added.

What does this information on Mu mean for clinical labs? Like other aspects of the COVID-19 pandemic, laboratorians probably should keep abreast of the latest news and research findings on Mu, just as they do for many other aspects of the rapidly evolving COVID-19 pandemic.

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

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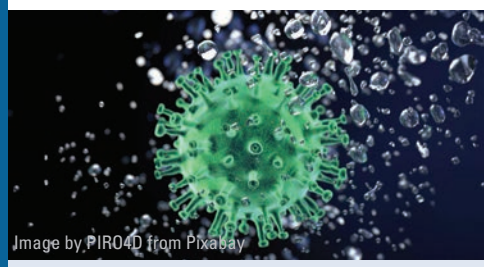
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Fast Facts

COVID-19 and Kidney Disease Risk

The Washington University School of Medicine in St. Louis reported on a COVID-19 long hauler's risk of kidney disease.

90%
of people with ailing kidneys don't know it

> 38 million
people have been diagnosed with COVID-19 since the pandemic started

510,000
of people who had COVID-19 may have kidney injury or disease

30%
higher risk of developing acute kidney injury if contracted COVID-19 and not hospitalized

215%
higher risk of acquiring end-stage kidney disease for non-hospitalized COVID-19 patients

7X
risk of major adverse kidney event if hospitalized with COVID-19

13X
the risk of end-stage kidney disease if hospitalized with COVID-19

5.3%
have a decrease of 30% or more in glomerular filtration rates (GFR) after a month of COVID-19

Source: https://medicine.wustl.edu/news/covid-19-long-haulers-at-risk-of-developing-kidney-damage-disease/

AI blood testing technology can detect lung cancers

An artificial intelligence (AI) blood testing technology developed by researchers at the Johns Hopkins Kimmel Cancer Center was found to detect more than 90% of lung cancers correctly in samples from nearly 800 individuals with and without cancer.

The test approach, called DELFI (DNA evaluation of fragments for early interception), spots unique patterns in the fragmentation of DNA shed from cancer cells circulating in the bloodstream. Applying this technology to blood samples taken from 796 individuals in Denmark, the Netherlands and the U.S., investigators found that the DELFI approach accurately distinguished between patients with and without lung cancer.

Combining the test with analysis of clinical risk factors, a protein biomarker, and followed by computed tomography imaging, DELFI helped detect 94% of patients with cancer across stages and subtypes. This included 91% of patients with earlier or less invasive stage I/II cancers and 96% of patients with more advanced stage III/IV cancers.

The DELFI technology uses a blood test to indirectly measure the way DNA is packaged inside the nucleus of a cell by studying the size and amount of cell-free DNA present in the circulation from different regions across the genome. Healthy cells package DNA like a well-organized suitcase, in which different regions of the genome are placed carefully in various compartments. The nuclei of cancer cells, by contrast, are like more disorganized suitcases, with items from across the genome thrown in haphazardly. When cancer cells die, they release DNA in a chaotic manner into the bloodstream.

DELFI helps identify the presence of cancer using machine learning, a type of artificial intelligence, to examine millions of cell-free DNA fragments for abnormal patterns, including the size and amount of DNA in different genomic regions. This approach provides a view of cell-free DNA referred to as the "fragmentome." The DELFI approach only requires low coverage sequencing of the genome, enabling this technology to be cost-effective in a screening setting.

The DELFI approach found that patients who were later determined to have cancer had widespread variation in their fragmentome profiles, while patients found not to have cancer had consistent fragmentome profiles.

High virus count in the lungs drives COVID-19 deaths

The buildup of coronavirus in the lungs is likely behind the steep mortality rates seen in the pandemic, a study finds. The results contrast with previous suspicions that simultaneous infections played major roles in heightened risk of death, according to a news release from NYU Langone Health.

Led by researchers at NYU Grossman School of Medicine, the study shows that people who died of COVID-19 averaged 10 times the viral load in their lower airways as did severely ill patients who survived their illness. Investigators found no evidence implicating a secondary bacterial infection as the cause of the deaths, but they cautioned this may from frequent antibiotics given to critically ill patients.

Current guidelines from the Centers for Disease Control and Prevention (CDC) do not encourage the use of antivirals, such as remdesivir, for severely ill patients on mechanical ventilation. The NYU Langone study results suggest that these medications may still yet remain a valuable tool in treating these patients, though more researcher may be needed.

Despite previous concerns that the virus may prompt the immune system to attack the body's own lung tissue and lead to dangerous levels of inflammation, the investigators found no evidence that this was a major contributor to COVID-19 deaths in the group studied. In fact, researchers said that the strength of the immune response appeared proportionate to the amount of virus in the lungs.

COVID-19 patients placed on mechanical ventilators in order to breathe fare particularly poorly, with 70 percent nationwide succumbing to the illness. Notably, experts attribute the high mortality seen in other viral pandemics such as the Spanish flu in 1918 and swine flu in 2009 to a secondary bacterial infection. However, it remained unclear whether a similar issue affected people with COVID-19.

The study, recently published in *Nature Microbiology,* was to clarify the role of secondary infections, viral load, and immune cell populations in COVID-19 mortality.

However, the investigators only studied patients with coronavirus who survived their first two weeks of hospitalization. It is possible that bacterial infections or autoimmune reactions may play a greater role in COVID-19 mortality that occurs earlier.

NIH study shows no benefit from convalescent plasma for some COVID-19 outpatients

The final results of the Clinical Trial of COVID-19 Convalescent Plasma in Outpatients (C3PO) demonstrate that COVID-19 convalescent plasma did not prevent disease progression in a high-risk group of outpatients with COVID-19 when administered within the first week of their symptoms.

The trial was stopped in February 2021 due to lack of efficacy based on a planned interim analysis. The formal conclusions from the trial, which was funded primarily by the National Heart, Lung, and Blood Institute (NHLBI), part of the National Institutes of Health, and by the Biomedical Advanced Research and Development Authority (BARDA), part of the Office of the Assistant Secretary for Preparedness and Response at the U.S. Department of Health and Human Services, appear in the *New England Journal of Medicine.*

"We were hoping that the use of COVID-19 convalescent plasma would achieve at least a 10% reduction in disease progression in this group, but instead the reduction we observed was less than 2%," said Clifton Callaway, MD, PhD, the contact principal investigator for the C3PO trial and Professor of Emergency Medicine at the University of Pittsburgh.

Last year, the U.S. Food and Drug Administration (FDA) issued an emergency use authorization (EUA) to allow use of convalescent plasma in hospitalized patients with COVID-19. Researchers wanted to know whether administering COVID-19 convalescent plasma might also be beneficial in persons who were recently infected with SARS-CoV-2, the virus that causes the disease, but who were not severely ill and could be treated as outpatients. The objective was to prevent progression to severe COVID-19 illness.

The randomized, controlled clinical trial involved adult outpatients who presented to emergency departments with mild COVID-19 symptoms during their first week post-infection and had at least one risk factor for progression to severe COVID-19, such as obesity, hypertension, diabetes, heart disease, or chronic lung disease. They were randomly assigned to receive treatment with either high-titer COVID-19 convalescent plasma (containing anti-COVID-19 antibodies) or placebo (salt solution infused with multivitamins and lacking antibodies). The researchers found no significant difference in disease progression between the two groups.

CDC study finds unvaccinated people nearly 5 times more likely to get COVID-19

People who are not vaccinated against COVID-19 are 4.9 times more likely to get COVID-19 and the 29.2 times more likely to be hospitalized than fully vaccinated people, the Centers for Disease Control and Prevention (CDC) reported in its Morbidity and Mortality Weekly Report (MMWR). That was based on data from Los Angeles County on July 25, when the Delta variant was pervasive.

Among 43,127 reported SARS-CoV-2 infections in residents at least 16 years of age, 10,895 (25.3%) were in fully vaccinated people, 1,431 (3.3%) were in partially vaccinated people, and 30,801 (71.4%) were in unvaccinated people.

Fewer fully vaccinated people infected with SARS-CoV-2 were hospitalized (3.2%), admitted to an intensive care unit (0.5%), and required mechanical ventilation (0.2%), compared with partially vaccinated people (6.2%, 1.0%, and 0.3%), and unvaccinated people (7.6%, 1.5%, and 0.5%).

During May 1-July 25, the percentages of B.1.617.2 (Delta) variant infections estimated from 6,752 samples with lineage data increased among fully vaccinated persons (from 8.6% to 91.2%), partially vaccinated persons (from 0% to 88.1%), and unvaccinated persons (from 8.2% to 87.1%).

Whole genome sequencing (WGS)-based SARS-CoV-2 lineages and cycle threshold (Ct) values from qualitative reverse transcription-polymerase chain reaction (RT-PCR) for two SARS-CoV-2 gene targets, including the nucleocapsid (N) protein gene region and the open reading frame 1 ab (ORF1ab) polyprotein gene region, were reported for a sample of the specimens.

CDC and FDA collaborate on Antibiotic Resistance Isolate Bank

The U.S. Food and Drug Administration (FDA) and the Centers for Disease Control and Prevention (CDC) have teamed up to create a repository of resistant bacterial and yeast isolates of national medical concern that have been phenotypically and genotypically characterized.

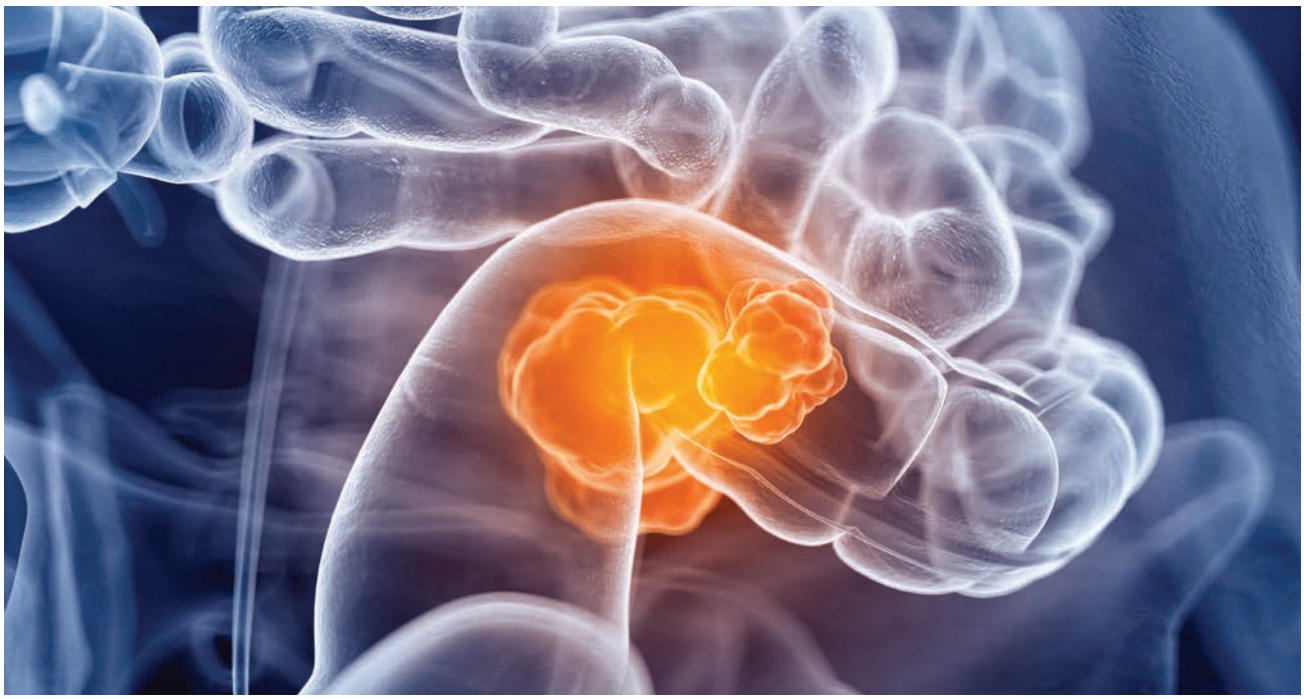
Called the Antibiotic Resistance Isolate Bank (AR Isolate Bank), it contains isolate panels that are available free of charge as a resource for developing drugs and diagnostic testing panels.

Routinely updated, the AR Isolate Bank has new resistant isolates and their corresponding resistance markers. The isolates are preassembled into panels and upon request, isolates and/or panels are shipped to diagnostic and pharmaceutical companies, academia, as well as clinical and public health laboratories. For example, academic medical centers or private and reference laboratories may use the panels and isolates to create lab developed tests (LDTs).

As of February 2021, the bank had 29 panels and 952 isolates.

Available panels and ordering instructions can be found on the AR Isolate Bank on CDC.gov and can be used in development of diagnostic tests and in studies; however, the FDA will also accept premarket submissions that use well-characterized isolates from other sources. The isolates in the AR Isolate Bank may be helpful in challenging tests for the detection of infectious diseases and their associated resistance mechanisms, as well as antimicrobial susceptibility testing devices, to ensure the tests can efficiently detect a variety of resistant microorganisms and/or molecular markers of resistance.

Derived from various specimen sources and emerging resistance mechanisms, the isolates in the AR Isolate Bank are from healthcare-associated and community-associated infections, foodborne illnesses, and sexually transmitted infections, such as gonorrhea. Each isolate is verified for purity and identified using matrix-assisted laser desorption-ionization time of flight mass spectrometry (MALDI-TOF MS) and 16S rRNA gene sequencing (as needed). Antimicrobial susceptibility testing (AST) is performed using the reference broth microdilution method in accordance with Clinical and Laboratory Standards Institute (CLSI) standards. In addition, whole genome sequencing is performed on isolates to identify resistance markers and to better understand the genotypic basis of resistance.



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Advances in colorectal cancer therapeutic biomarkers

By Ajay Prakash, MD, PhD, and Subbaya Subramanian, MS, PhD

Colorectal cancer (CRC) remains a significant public health burden in the U.S., estimated to be the fourth leading cause of cancer diagnosis but the second leading cause of deaths in 2021.[1] This mortality deficit is driven largely by the limited treatment options and poor disease control seen in the advanced stages of cancer, where chemotherapy is still the primary treatment modality.

Insights into molecular subtyping of cancers including colon, breast, and prostate, along with the discovery of so-called 'driver' mutations, have significantly advanced targeted and immune therapies for these cancers. Yet, the success of targeted therapies in CRC remains limited, and their utility remains primarily as an adjunct to mainline chemotherapy, or as a salvage treatment, which is a therapy used after others have failed to produce results.

However, a number of recent clinical trials have sought to change that, bringing targeted and immune therapies into earlier lines of treatment. In addition, a number of recent translational studies have demonstrated promising early results in the sensitization of CRC to existing targeted or immune treatments. Through sensitization, tumors that historically would not respond to immunotherapy treatments may be converted to responders. Given the durability of response seen in most immune therapies, this represents a significant therapeutic promise.

In this article, we will review the current standards of care regarding tests and treatments for therapeutic biomarkers, with particular attention to immune therapies, including a novel approach, which uses extracellular vesicles (EV's), or lipid bound vesicles secreted into extracellular space by cells, to sensitize CRC to immunotherapy treatments.

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LEARNING OBJECTIVES

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

1. Describe the current standards of care regarding tests and treatments for colorectal cancer.
2. Differentiate how immune therapies can impact colorectal cancer.
3. Discuss a novel approach using extracellular vesicles (EV's) to sensitize CRC to immunotherapy treatments.
4. List the biomarkers associated with colorectal cancer.

Standard of care testing for therapeutic biomarkers

As with all cancers, the selection of a standard treatment for CRCs depends largely on the clinical and pathological stage. Treatment for early-stage colon and rectal cancers, which are potentially curable, relies on local therapies, including surgery and radiation. In later-stage cancers, providers also may add chemotherapy or targeted therapies.

Biomarker testing is of limited utility in localized colon cancer, with only microsatellite instability (MSI) testing recommended. MSI occurs when there is a cellular change to the number of repeated DNA bases in a microsatellite, or a repeated DNA

Term	Impact in colorectal cancer
BRAF mutations	Specific phenotype and metastasis; resistance to anti-EGFR mAb; test amplification of HER2 gene
EGFR	Involved in cell signaling, may cause cancer cells to divide faster
EVs	Induced expression of PD-LV1 leads to tumor immunosuppression, increased ICD responsiveness
KRAS mutations	Heterogeneity of CRC; resistance to anti-EGFR mAb; test amplification of HER2 gene
Micro-RNA	Early detection of CRC, prognostic stratification and therapy-response prediction
MSI	Resistance to 5-FU; marker for DNA repair deficiencies; ICB response
NTRK fusions	Cancer cell differentiation, specifying sensory neuron subtypes; enriched in MSI-high populations
HER2	Increased HER2 causes cancer to grow and spread; human epidermal growth factor receptor 2
ICB	Immune checkpoint blockade; inhibitor drugs block proteins to help T-cells function
PD-L1	Protein controlling immune response; if binds with another protein, T-cells are hampered
CTLA4	Antibodies targeting the immunosuppressive CD80/86 receptor on T-cells
CD28	Immunoglobulin, receptor for CD80 and CD86; simulates T-cells and can provide signal to produce interleukins
CD 80	Immune cell protein causes T-cells to make substances to help control immune response; upregulated on B cells by cytokines
CD 86	Immunoglobulin, membrane protein expressed by antigen-presenting cells; ligand for proteins of T-cells; upregulated on B cells
miR-424	MicroRNA that binds to messenger RNAs to block them from making proteins, regulates cancer behavior

Table 1. CRC Terms
Source: cancer.gov (See reference 16)

sequence, from how it was originally inherited. Knowing whether a cancer has MSI helps when forming a treatment plan. For example, MSI testing is used primarily as a screening tool for Lynch Syndrome, which is the leading cause of hereditary colorectal cancer. [2]

Much broader testing is recommended in the unresectable or metastatic setting, where MSI status, along with mutations in the genes KRAS and BRAF are evaluated, as are amplifications of the gene HER2, or fusions of the NTRK gene. Of these biomarkers, KRAS, NTRK, and MSI have all been associated with immunomodulation or immunotherapy response, making them promising targets for therapy for patients with metastatic colon cancer. (See **Table 1**.)

KRAS mutations

KRAS testing has long been a prerequisite to the treatment of advanced CRC, primarily due to its relationship with the EGFR (Epidermal Growth Factor Receptor), a protein, tyrosine kinase, that binds to the epidermal growth factor and is involved in cell signaling pathways for cell division. Mutations in the EGFR gene cause proteins to be made more than normal on some cancer cells, which causes the cancer cells to divide faster. The KRAS gene creates a protein involved in cell signaling; thus, mutations to the KRAS gene may also cause cancer cell growth. KRAS mutations are among the most common alterations found in CRC.[3]

Anti-EGFR antibodies, like cetuximab, have been shown to be effective in combination with chemotherapy in the treatment of advanced CRC.[4] KRAS mutations in CRC tend to be constitutively activating; meaning, upstream EGFR inhibition has no effect on its signaling, rendering anti-EGFR antibodies ineffective in the treatment of KRAS mutant tumors.

Thus, for over a decade, KRAS has played a key role as a predictive biomarker in colorectal cancer treatment.

More recent studies have looked to expand the role of immunotherapies by allowing direct targeting of mutant KRAS. Multiple pre-clinical studies, along with early phase clinical trials, have demonstrated the efficacy of inhibitors of specific KRAS mutants in multiple solid tumor types.[5] With the recent approvals by the U.S. Food and Drug Administration (FDA) of KRAS G12C mutant inhibitors, such as sotorasib, in lung cancer, and preliminary evidence of efficacy against this same mutation in CRC, targeted therapies for KRAS-mutant CRC may soon become the standard of care.

NTRK fusions

NTRK fusions take place when a piece of the chromosome with the NTRK gene breaks off and joins with a different gene on another chromosome, leading to abnormal proteins known as TRK fusion proteins, which cause cancer growth. This is also known as neurotrophic tyrosine receptor kinase gene fusion.

Fusions of NTRK are much rarer in CRC, compared with other types of cancer, comprising less than 1% of advanced cancer cases. Recently, the FDA approved a highly efficacious inhibitor for use in all cancer types where this fusion is found.[6] Though NTRK mutations are considered to be mutually exclusive with KRAS, there are some data to suggest that RAS protein mutations may be a potential resistance mechanism to NTRK fusion inhibition.

Biomarkers and immunotherapy

Of note, NTRK fusion-positive CRC appears to be enriched for microsatellite instability (MSI-high) and a high tumor mutational burden (TMB-high).[7] NTRK fusions are also enriched within the MSI-high population, though the rarity of both biomarkers leaves the number of studied patients low.[8] Further, several studies have demonstrated that RAS protein mutation leads to immunosuppression and reduced immune infiltration.[9] Thus, a greater understanding of the tumor immune environment and immunotherapy, in general, may aide in treatment of multiple biomarker-driven diseases.

MSI and immunotherapy

Testing for microsatellite instability, a marker for DNA repair deficiencies and a CRC-specific immune checkpoint blockade (ICB) response, is currently recommended for all stages of colorectal cancer. Immune checkpoint inhibitors are drugs that

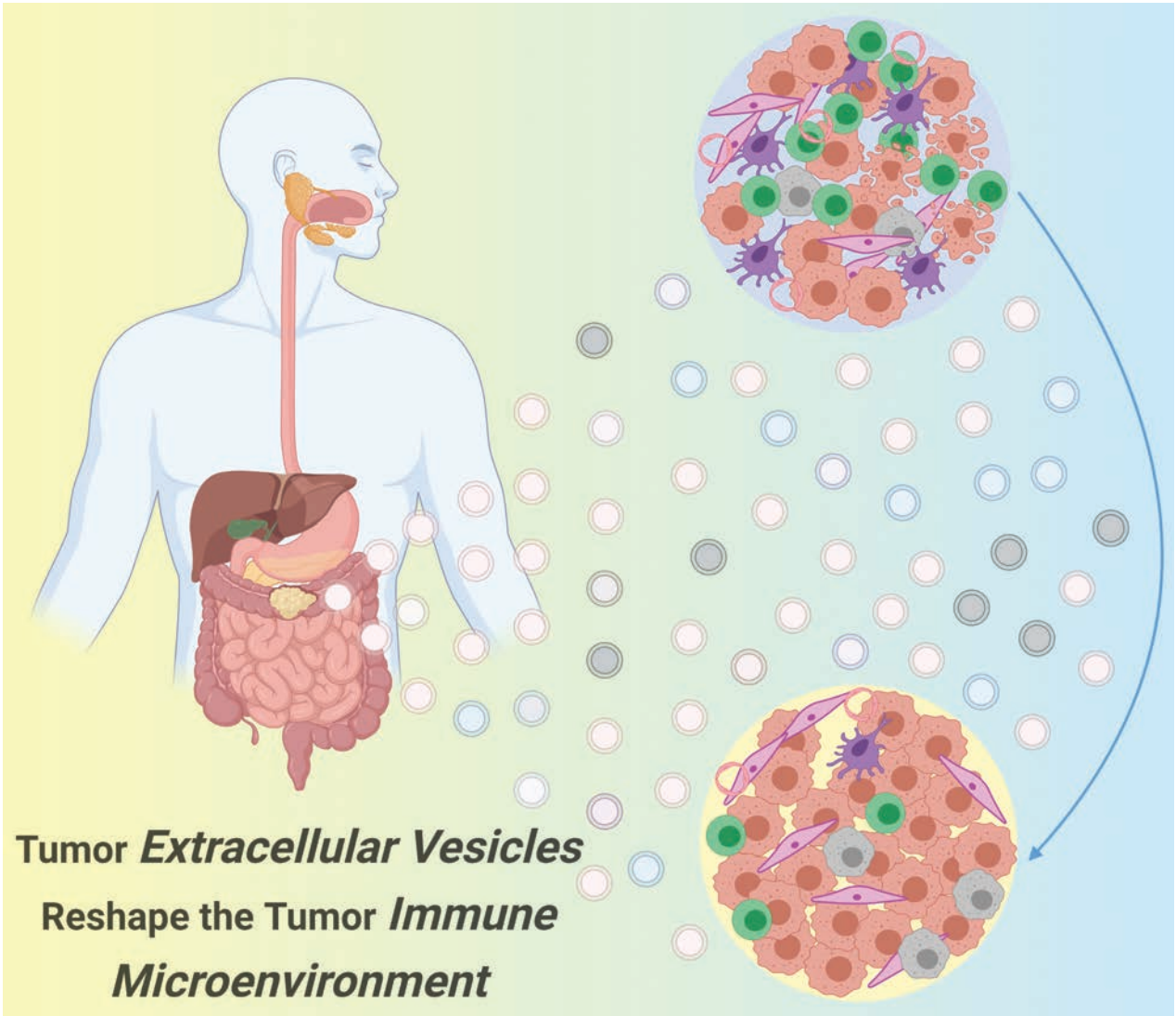

Figure 1. 3D rendering of T cells with cancer cells, courtesy of University of Minnesota.

block the proteins involved in regulating the checkpoints of the immune cascade, which are triggered by some cancer cells to suppress immune responses and inhibit T-cells from killing cancer cells. Blocking these checkpoints helps T-cells function.

While TMB-high status is also an approved indication for ICB treatment in solid tumors, the response rates for TMB-high patients in CRC is poor, ranging from 4-14%, and testing is not recommended by the National Comprehensive Cancer Network (NCCN). Yet, even within the MSI-high patient population, response rates to ICI therapy can be below 50%. Further complicating the picture, one recent study suggests that a subset of heavily pretreated metastatic microsatellite stable (MSS) colorectal cancer, without liver metastases, may also respond to ICB therapy.[10]

Given these conflicting data, and mediocre ICB response rate in MSI-high CRC, significant efforts are being made to understand what aspects of the tumor microenvironment may affect ICB treatment response. Multiple recent studies have suggested that extracellular vesicles (EVs), lipid-bilayer particles involved in numerous physiologic processes, could be utilized to induce ICB response.[11, 12, 13, 14] In particular, the work by Zhao and colleagues, evaluating the role of EVs in modulated T-cell and ICB response, represents a promising new avenue of investigation.

Extracellular vesicles and the CD28-CD80/86 axis

Small EV's, sometimes termed exosomes, have long been understood to play a variety of roles in tumorigenesis and cancer progression, including extracellular membrane remodeling, angiogenesis, tumor invasion, treatment resistance, and immunosuppression. Yet, only recently have we understood how to modulate these relationships and subsequent tumor ICB response.[11] One important study examined PD-L1, a protein that helps keep the body's immune responses under control, and when it binds with another protein, it keeps T cells from killing cancer cells.

Chen and colleagues found that induced expression of PD-L1 in EVs using IFN-γ, a dimerized soluble cytokine in the type II class of interferons, led to tumor immunosuppression, which, in turn, increased responsiveness to ICB therapy. Yet, treatment options for PD-1/PD-L1 ICB refractory disease are limited, which has led to significant research into additional T-cell immunosuppression pathways.

Indeed, CTLA4 antibodies targeting the immunosuppressive CD80/86 receptor on T-cells have been shown to be effective in treating numerous immunotherapy-sensitive solid tumors.

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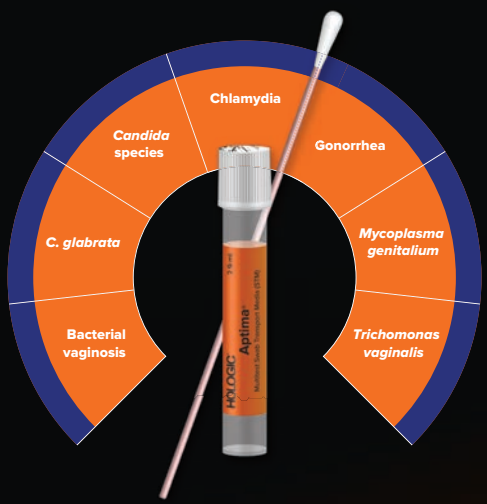

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But these therapies have not proven as effective as PD-1/PD-L1 targeted therapies, and recent studies have suggested that the CD 80/86 co-receptor CD28 may be a better target for inhibition.[15] Thus, Zhao and colleagues investigated whether EV's could be utilized to modulate the CD28-CD80/86 axis and increase T-cell cytotoxic activity against colorectal cancer.

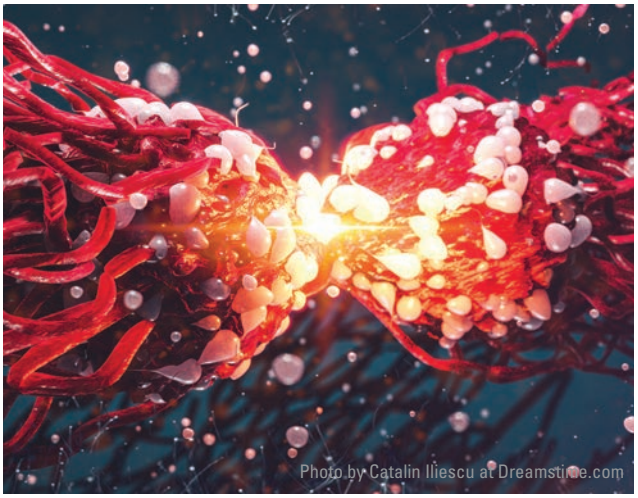
In their study, Zhao and colleagues first identified that the CD28-CD80/86 axis was dysregulated on tumor infiltrating T-cells and dendritic cells, though the expression levels were surprisingly invariant between microsatellite stable (MSS) or MSI tumors. Using genetic knockout mice, they found that the absence of CD28 and CD80/86 prevented colorectal cancer xenograft (a tissue graft from a donor of a different species) response to ICB therapy. Then, utilizing a microRNA (miRNA) screen of miRNAs specifically overexpressed in CRC, they identified miR-424 as a negative regulator of the CD28-CD80/86 pathway, suggesting that this miRNA may be at least partially responsible for tumor immunosuppression.

The authors found that tumor-derived EVs are a significant mechanism for delivery of miR-424 to its T-cell and dendritic cell targets. Then, using miR-424 knockout tumors, the authors showed that these tumors generated EVs without miR-424, and that this absence leads to immune-driven tumor suppression (See **Figure 1**.).

Finally, the authors found that these miR-424 absent EVs could then be administered to a separate xenograft, and lead to significantly improved ICB efficacy against those tumors. Thus, the authors established that miRNA depleted or absent EVs may be a critical adjunct in CRC ICB therapy, leading to rescue of treatment resistance, or the induction of treatment response in the vast majority of CRC that does not respond to ICB therapy.

Conclusions

There have been significant advances in the targeted treatment of therapeutic biomarkers in CRC, especially as related to immunotherapy. However, we are still developing our understanding of tumor characteristics that affect treatment, and the optimal modalities with which they can be paired. While exciting advances are being made in multiple avenues, the results presented by Zhao and colleagues, utilizing modified extracellular vesicles are unique in multiple respects. They represent a mutation agnostic methodology by which CRC may be sensitized to immunotherapy, regardless of molecular subtype or location of metastases. In addition, their study involved the usage of tools that are already in clinical investigation. Given promising results from multiple early phase EV clinical trials, these data may present a novel therapeutic option for a large population of CRC patients for whom treatment options are currently limited.



3D rendering of a cancer cell dividing

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1. **Colorectal cancer (CRC) is estimated to be the _____ leading cause of cancer diagnosis but second leading cause of deaths in 2021.**
   - a. second
   - b. third
   - c. fourth
   - d. seventh

2. **What is the primary treatment modality for CRC?**
   - a. Liquid biopsy
   - b. Chemotherapy
   - c. Radiation
   - d. Dialysis

3. **What has significantly advanced targeted and immune therapies for these cancers?**
   - a. Hematology
   - b. Microscopy
   - c. Molecular subtyping of cancers
   - d. Fecal analysis

4. **A novel approach uses _____ to sensitize CRC to immunotherapy treatments.**
   - a. extracellular vesicles (EV's)
   - b. mitochondria
   - c. Golgi apparatus
   - d. ribosomes

5. **Treatment for early-stage colon and rectal cancer, which are potentially curable, relies on local therapies, including _____.**
   - a. surgery
   - b. radiation
   - c. chemotherapy
   - d. both A and B

6. **Later stage cancers may have additional _____ or targeted therapies added.**
   - a. surgery
   - b. radiation
   - c. chemotherapy
   - d. both A and B

7. **Only microsatellite instability (MSI) testing is recommended primarily as a screening tool for _____.**
   - a. Fournier's Syndrome
   - b. Down's Syndrome
   - c. Irritable Bowel Syndrome (IBS)
   - d. Lynch Syndrome

8. **Much broader testing is recommended in the unresectable or metastatic setting, where MSI status, along with mutations in the genes _____ are evaluated.**
   - a. BRCA and TCGA
   - b. MSI and CST1
   - c. EGFR and TIBC
   - d. KRAS and BRAF

9. **KRAS, NTRK, and MSI have all been associated with _____.**
   - a. inflammation
   - b. immunomodulation
   - c. mortality
   - d. breast cancer

10. **In the unresectable or metastatic setting, providers test for amplifications of the _____ gene.**
    - a. HER2
    - b. BRCA
    - c. TCGA
    - d. CST1

11. **KRAS testing has long been a prerequisite to the treatment of advanced CRC, primarily due to its relationship with the _____.**
    - a. BRCA
    - b. TIBC
    - c. EGFR
    - d. CST1

12. **_____ mutations are among the most common alterations found in CRC.**
    - a. Colon
    - b. Duodenum
    - c. BRCA
    - d. KRAS

13. **Anti-EGFR antibodies, like_____, have been shown to be effective in combination with chemotherapy in the treatment of advanced CRC.**
    - a. cetuximab
    - b. sIgA
    - c. ab9141
    - d. cystatin SN

14. **KRAS mutations in CRC tend to be constitutively activating, meaning that upstream _____ inhibition has no effect on its signaling.**
    - a. TIBC
    - b. BRCA
    - c. CST1
    - d. EGFR

15. **There has been recent approval of _____ mutant inhibitors in lung cancer.**
    - a. BRCA
    - b. KRAS G12C
    - c. CST1
    - d. TIBC

16. **Fusions of _____ are much rarer in CRC, comprising less than 1% of advanced cancers.**
    - a. KRAS
    - b. EGFR
    - c. NTRK
    - d. BRCA

17. **Some data suggests that RAS protein mutations may be a potential resistance mechanism to _____ fusion inhibition.**
    - a. BRCA
    - b. EGFR
    - c. CST1
    - d. NTRK

18. **_____CRC appears to be enriched for microsatellite instability (MSI-high) and a high tumor mutational burden (TMB-high).**
    - a. NTRK fusion-positive
    - b. CST1 fusion-negative
    - c. High-grade large cell
    - d. Small cell neuroendocrine

19. **Multiple recent studies have suggested that extracellular vesicles (EVs), lipid-bilayer particles involved in numerous physiologic processes, could be utilized _____.**
    - a. for fecal biopsies
    - b. to induce ICB response
    - c. to stabilize the colon
    - d. to prevent liver metastasis

20. **Expression of PD-L1 in _____ using IFN-γ led to tumor immunosuppression, which, in turn, increased responsiveness to ICB therapy.**
    - a. evasomes
    - b. ribosomes
    - c. mitochondria
    - d. exosomes

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   P ① ② ③ ④ ⑤ E
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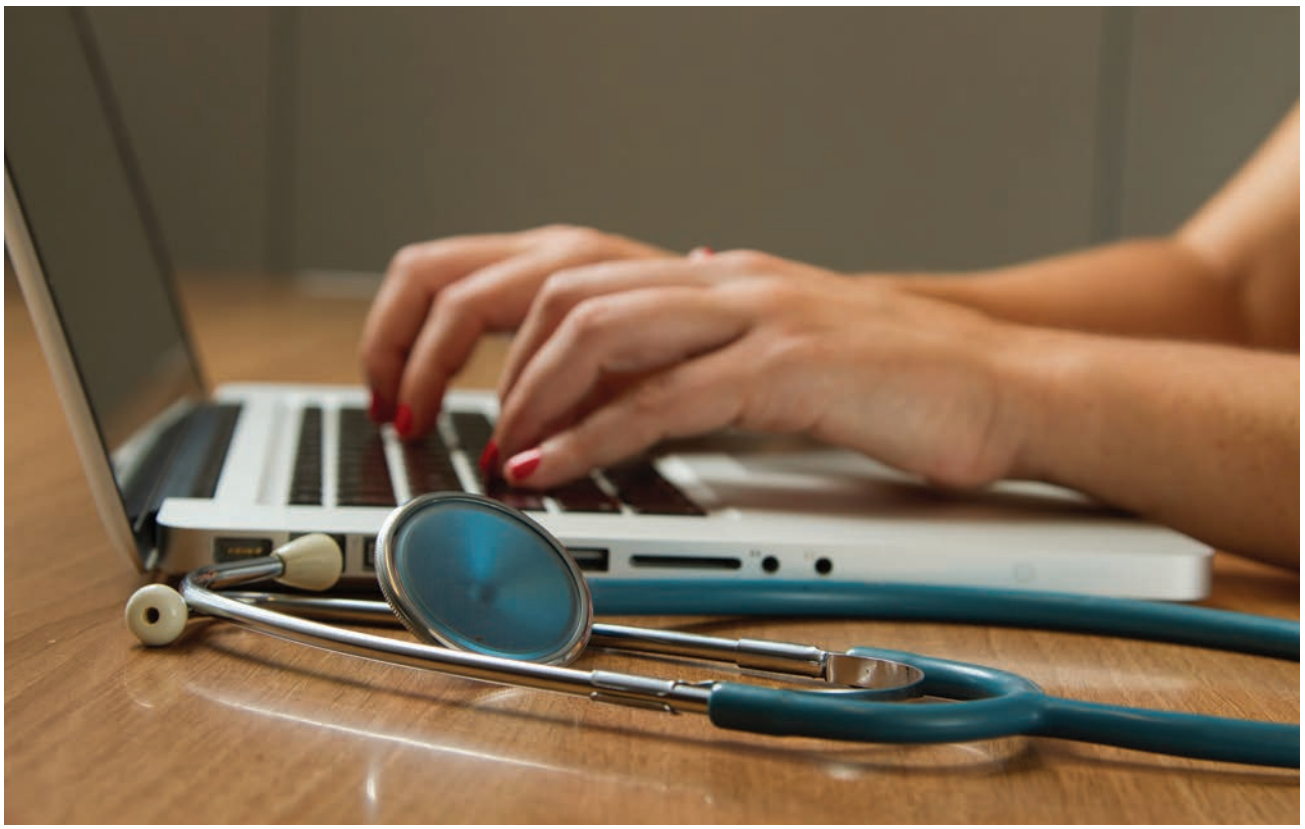

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Recapturing revenue by upgrading your lab's outreach strategy post-COVID-19

By Marci Dop

While COVID testing is likely here to stay for the long term, labs are starting to feel the pinch of reduced testing revenue. To solve that problem and maintain or increase market share, labs should ensure their outreach program is meeting the needs of current customers and has the flexibility to appeal to new ones.

Whether your lab is in a hospital, fully independent, or specializes in one clinical area, outreach should play an important role in your lab's revenue strategy. What makes a provider, and sometimes the patients themselves, choose a lab? Convenience. A lab's processes and outward-facing information should be so simple and straightforward that the potential customer doesn't think twice about making the choice.

Providers and staff across the industry are experiencing severe burnout after more than 18 months of the COVID-19 pandemic. Lab staff are undoubtedly feeling fatigue as well. Fighting to send an order or receive results from a laboratory is another burden that no one has the time to hassle with. If it is difficult for the customer to send the lab an order, it's likely that lab may lose the customer.

Building a laboratory outreach program

When building a competitive outreach program for a lab, the first goal in sight is to ensure that the processes for working with your laboratory will give you a competitive advantage. Yes, your tests need to be properly conducted, and your accuracy must be above question, but working with a laboratory should not add to the workflow of providers or their staff. How can this be accomplished? Through technology.

If your outreach program is competitive, requisitions should not be on paper. A fast-food hamburger is $2, and the process to order one is digital from beginning to end. Yet, in some laboratories where pathology tests can cost of hundreds of dollars, the order is still handled on paper. This makes no sense. Paper orders impact the quality of the order when they come with missing information, bad data, or just poor handwriting.

Aside from the impact on the accuracy of paper and manual processes, labs with paper processes are severely hindered in their ability to scale their outreach program and remain competitive in crowded markets.

To support the needs of the outreach program, laboratories must surround their customers with a suite of applications beyond the laboratory information system (LIS) or electronic health record (EHR). First, they require a robust physician connectivity package. When a medical practice is brought on as a new customer of the lab, delays in managing the connection allow time for that office to reconsider its decision.

For one west coast lab, the accessioners' desks were drowning in paper orders, making the lab unable to scale its outreach to take on new clients. Prior to the decision to make a technology

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upgrade, the lab was receiving more than 80% of its orders on paper. The process was manual and slow, making it so that order errors had to be corrected, costing precious staff time.

The lab's goal is to go from 80% of its orders being on paper to under 20% within the next twelve months. This ambitious goal was set, despite the lab's tandem objective of scaling operations and outreach to take on new customers. How will the lab do it? Through technology.

The first step for a lab taking on a new customer is to connect to the customer's EMR very quickly. The previously referenced west coast lab adopted an interface solution, which provided one central point of management for all orders and results. This streamlined processes for both the lab and the customer, simplifying the workflows on both ends. This workflow efficiency step will be one of the main strategies in achieving the goal of having less than 20% of orders on paper.

IT functions for outreach program

If a lab's outreach program has centralized applications that surround the LIS/EHR, they should be tailored to meet the needs of individual customers. Some of the IT functions needed for a good outreach program include:

- Flexibility in billing capabilities, so they are compatible across customers' unique systems.
- Vendor agnosticism, so a lab can quickly connect to clients for orders and results, regardless of the EMR vendor.
- A strong partnership with the hospital's IT support team.
- Service-level agreements in place with the contracting and compliance departments whenever possible, so any new clients requiring contracts or business associate agreements are turned around in a timely manner.

Throughout this pandemic, we have seen the need for connectivity in the lab on an unprecedented scale. These past few years have likely convinced labs of the need to invest in electronic connectivity to their customers. Labs that made technology investments during the pandemic were able to scale their testing and take on more clients. Those same labs can move into testing for more infectious diseases as well.

Unfortunately, the pandemic is not slowing down. If labs still haven't invested in enhanced connectivity, now is the time.

Additional connectivity to be competitive

It has been said repeatedly that labs must get out of paper ordering and go digital. While this is true, it's also not enough. To be competitive when doing outreach as a lab, that connectivity should go beyond just an interface for orders and results.

A good test of the connectivity between the lab and customer is the patient registration process. The lab's suite of applications should be able to capture payer information, patient demographics, and physician codes. If the EMR doesn't allow labs to ask questions when a lab order is added to the system, the deficiency should be made up for with a lab product.

Labs cannot rely on the physician practices, manual processes, or the orders/results interface to retrieve accurate patient insurance information. This is especially true for labs with large, varied client bases because there are several hundred EMR vendors. This lack of consistency makes verifying insurance a big challenge for laboratories.

Labs need to make managing insurance and test-compendium mapping simple. The suite of applications the labs use for connectivity should provide the ability to offer bridging capabilities to a practice's EMR. This will allow a lab to manage, maintain, and cross-reference information, such as insurance codes, test codes, and LOINC codes, while also providing on-demand mapping from third-party applications.

Automating these insurance processes eliminates the laborious manual cross-referencing, callbacks, and faxes to the physician's office to correct insurance information, so the lab can receive payment.

On the other side, physicians want results in multiple formats. For labs to be competitive, they should be able to easily deliver the results in whatever format their customers ask for.

A common functionality request is for labs to copy physicians on the lab results ordered by another treating physician treating a patient. Physicians also expect labs to have break-the-glass capability on results delivery, allowing those physicians to quickly gain access to restricted results data. Additionally, with the increasing prevalence of value-based care, physicians often request a longitudinal view of patient results for an isolated condition, allowing them to see a history of the results for the patient, but not all the tests that are unrelated to the diagnosis.

There are several flexibility offerings from vendors of interface products that labs must consider when evaluating what connectivity to offer their customers. First, labs need the ability to store patients' demographic information, so it can be sent to and from various entities. Second, it is essential to be able to pass orders from the EHR to the LIS or to any downstream reference laboratory. In addition to passing orders downstream, labs should be able to share results with any downstream entity needing them, including reporting to state agencies, and providing results to both providers and patients. Ideally, labs should offer electronic portals for both clinicians and their patients. And finally, labs should consider building rules-based routing, load balancing and mapping tools for insurance and test codes.

The lab's connectivity package ideally also should include the ability to print laboratory-branded requisitions at the medical practice as soon as the electronic EMR order is sent. This allows the processing staff to always know where to find information on the requisitions. Inconsistency in requisitions is one of the number one reasons for missed tests and missed test information. Specimen-ready labels reduce mislabeling of specimens and save time for the practice and laboratory staff.

Now is the time for labs to invest in outreach through technology. Not only can increased connectivity help labs solve reimbursement challenges with tools for clean orders, but they can increase their market share and return on investment by making lab ordering and test resulting easy for their customers.

Marci Dop is a lab industry expert and former lab CIO. Currently, she is a Strategic Advisor for **ELLKAY**.

Photo courtesy of Ortho Clinical Diagnostics

Navigating blood banking's 'perfect storm' of blood shortages

By: Andrew Corkum, MBA

While data on the prevalence of COVID-19 tests, confirmed cases and deaths are widely reported, another critical pandemic-related metric has stayed under the radar: the nation's available blood supply has shrunk dramatically during this time period, placing ever greater demands on blood banking professionals throughout the United Sates.

The American Red Cross reports that while individuals avoided making donations out of fear of potential exposure to the highly infectious SARS-CoV-2, demand for blood became greater than ever. Elective surgeries that had been postponed over the past year are now being rescheduled at the same time that hospitals are dealing with exceptionally high numbers of traumas and emergency department visits, with red cell demand up 10% this year alone.[1]

The eye of the storm: unprecedented demand, declining human resources

Further magnifying the impact of the blood banking industry's "perfect storm" is the pandemic's endless, overwhelming demands on frontline laboratory professionals, exhausting many seasoned laboratorians who may already have been anticipating retirement before the pandemic struck. In addition to processing extraordinary volumes of COVID-19 assays, transfusion medicine professionals also play a central role in screening and qualifying convalescent plasma donations as a potential emergency treatment for severely ill COVID-19 patients. But in addition to the physical risks of contracting the highly infectious and often deadly virus, as well as the physically taxing demands of working during the pandemic, Cabarkapa et al. noted that "emotional stress experienced by frontline healthcare workers is severe and can be enduring."[2]

Greenberg et al. stated that "healthcare staff are at increased risk of moral injury and mental health problems when dealing with the challenges of the COVID-19 pandemic."[3] At one major university health system, 1 in 5 healthcare workers reportedly was considering quitting because of the challenges of working during the pandemic, and an additional 30% of healthcare professionals were contemplating scaling back their work hours.[4]

The demands meted out by the COVID-19 pandemic again reinforced the urgent operational challenges clinical laboratories and blood banks were already experiencing as their everyday reality: addressing demands for increased throughput and efficiency, while simultaneously grappling with an ongoing shortage of trained, certified lab personnel.

The overall demand for blood testing was already increasing, as the global population ages and develops age-related health conditions, as well as multiple comorbidities.[5] Pre-pandemic, lab and blood bank managers across the U.S. were already grappling with human resource shortfalls, and the clinical laboratory workforce has been documented as declining over the past several years. In 2019, Garcia et al. reported that vacancy rates for laboratory positions for professionals across all departments had increased over the prior two years. Blood banks were among the most acutely affected by the workforce shortfall, projecting an anticipated 17.25% overall retirement rate — and perhaps even more concerning, a 27.99% projected retirement among lab supervisors — by the year 2023.[6]

Automation platforms enhance safety, efficiency

With the prevalence of newer and even more highly contagious variants of SARS-CoV-2, including Delta and Lambda, it is clear that the pandemic is continuing to tax healthcare delivery systems and clinical laboratory operations around the world. In light of the dual challenge blood banks are facing to fulfill growing clinical demands with a declining workforce of lab professionals, one viable solution may be automation,

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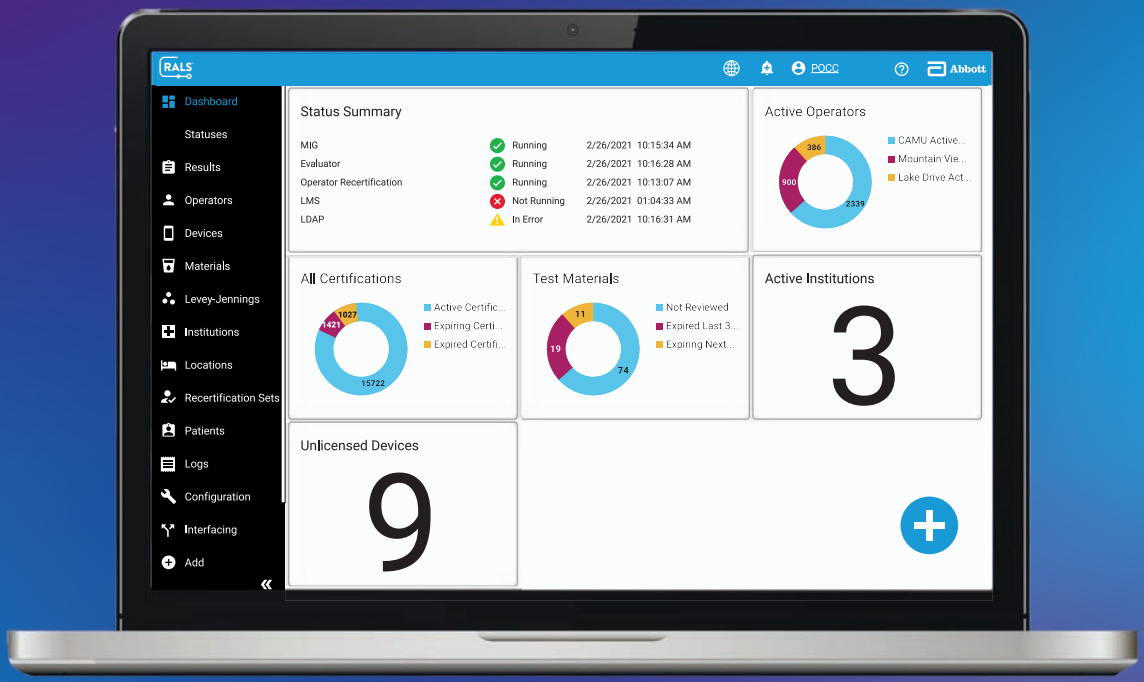

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including complete and semi-automated technology platforms that provide alternatives to manual tube testing and blood processing. As the need for rapid, efficient testing becomes ever more urgent, new automated and semi-automated diagnostic systems are now available that can help blood banks enhance efficiency, making it possible to automate more than 95% of all assays for patient blood samples. Networked systems are capable of accurately cross-matching blood with minimal waste, a consideration that is even more critical today due to the widespread donor blood shortage.

Even during pre-pandemic operations, human errors associated with manual pre-transfusion testing were a well-documented cause of transfusion-related mortality and morbidity. South et al. noted that most human errors can be eliminated by employing automated systems instead,[7] while Mistry et al. reported results from a meta-analysis indicating that 93% of ABO/D grouping errors, which could lead to dangerous and potentially catastrophic patient outcomes, involved manual pre-transfusion testing, while zero cases of such errors were found when full automation was used.[8]

Balbuena-Merle reports that when compared to manual techniques, automation in blood banking may help increase testing capability and throughput, while simultaneously reducing human resource staffing requirements and the potential for human coding errors. Automation also can promote standardization of results interpretation, increased transfusion safety, specimen batching and efficiency in turnaround times (TATs), and faster release of units, while simultaneously improving test reproducibility, traceability and patient identification.[9]

The benefits of automation are further supported in a 2000 briefing document published by the U.S. National Institutes of Health (NIH) in which the authors assert that the use of automation in clinical labs should not only increase testing accuracy, precision and significantly reduce TATs, but also potentially enhance employee productivity, physician satisfaction and drive greater efficiencies in the delivery of patient care with the redistribution of workload.[10]

Automation also may be beneficial in locations where testing is not being performed by trained and certified blood banking professionals, but rather by generalists working in core labs. In short, regardless of setting, automation platforms can allow serologists to shift their focus to the most critical cases that warrant their attention, while the automated systems ensure that the right unit is being tested, for the right patient, at the right time.

Evaluating automation's potential with workflow analysis and key metrics

Determining whether to adopt an automated approach in blood bank operations first involves clarifying the specific requirements of a site, which involves mapping a complete operational workflow to clearly understand which processes currently involve humans (such as handling, sorting, and distributing specimens), sample arrival patterns, current testing profiles, percent of routine versus non-routine testing, current footprint and lab setup, staffing patterns and so on. The workflow analysis typically identifies bottlenecks, waste, and other potential challenges that automation could address, and many independent consultants, as well as diagnostics systems manufacturers, perform these analyses.

In addition, it is also important to evaluate the applicability of automation by considering key performance metrics, such as average TAT; clearly defining operational processes, such as how STAT samples are categorized and prioritized; and evaluating whether sample storage and retrieval procedures might also benefit from automated approaches.[11]

Results reported with speed, efficiency and visibility

Finally, the newest lab automation solutions available today also feature integrated software programs that allow organizations of all sizes — from large university reference labs with multiple satellite operations, to small local, regional, or even neighborhood blood banks — to seamlessly access detailed data in real time with greater accuracy and visibility of results. Such systems facilitate consistent recording and secure storage of data, as well as instantaneous recall, review and analysis of results whenever needed, regardless of an institution's location or size of operation.

The pandemic may have accelerated the urgent need for automation in blood bank settings, but the benefits can be long-lasting. When specified and operated correctly, a fully or semi-automated system should be able to deliver measurable improvements in overall diagnostic performance, accuracy, throughput, quality and standardization, while also helping managers address staffing challenges and show progress toward achieving cost management and other performance-based goals.

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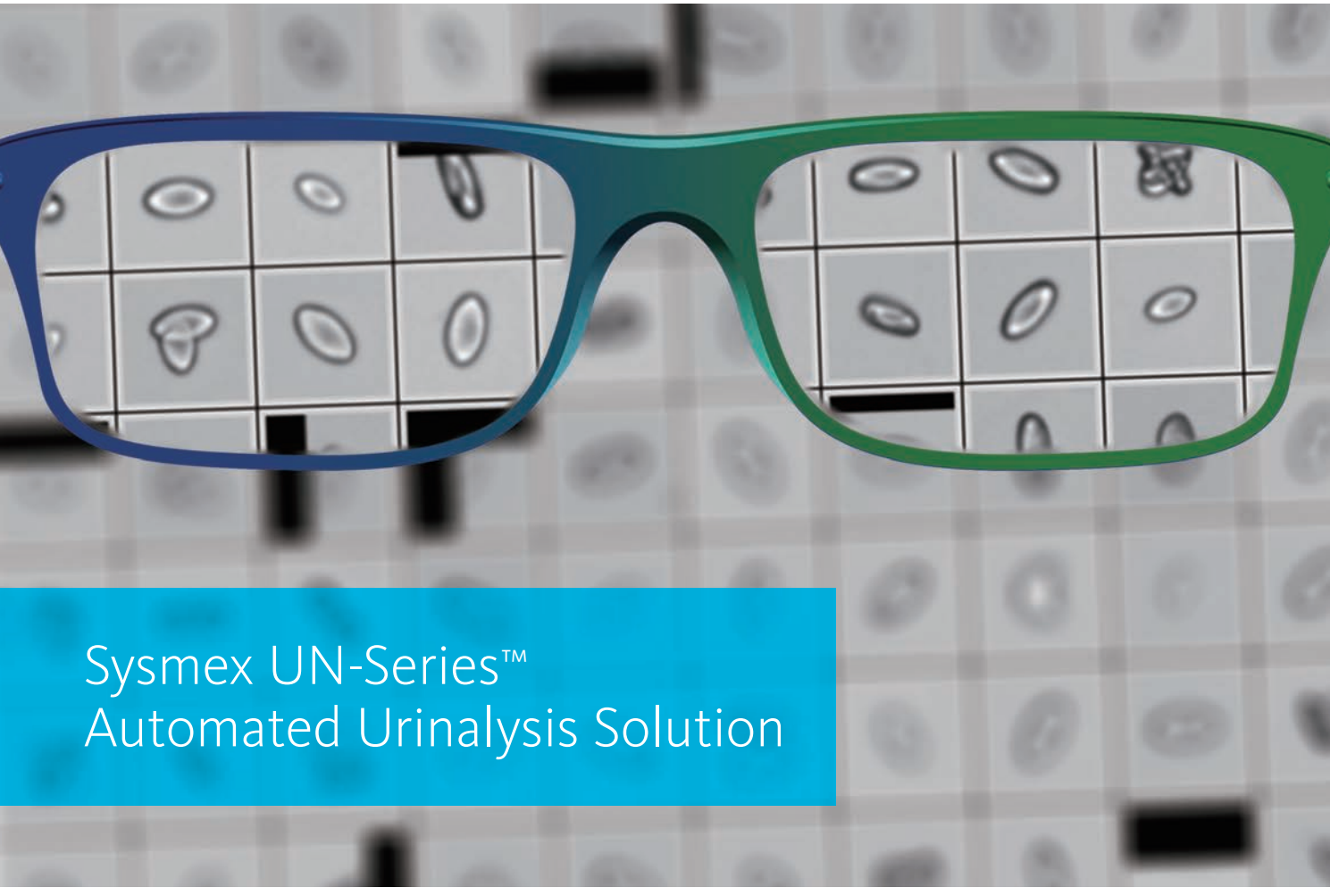

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Looking back and moving forward with COVID-19 lab safety

By Dan Scungio, MT (ASCP), SLS, CQA (ASQ

When it comes to managing a laboratory safety program, it is always favorable to utilize proactive indicators. The best approach is to use indicators and practices that can prevent safety issues in the department before they have a chance to occur. The reality is, however, that no safety program is without weaknesses, and injuries and exposures do happen from time to time. Most of these events are preventable, but occasionally, one occurs that — because of very unusual circumstances — could not be avoided. Whether an event is characterized as unavoidable or preventable, though, lessons can certainly be learned.

A similar logic can be applied to the COVID-19 pandemic. As laboratory leaders watched it spread across the world and make its way to our shores, it became clear that U.S. hospitals and laboratories would be affected in many, perhaps unprecedented ways. This would be an unavoidable event, and it would have far-reaching consequences. Now, more than 18 months later, laboratory leaders can look back at the many lessons learned during the pandemic. As the world moves ahead to contend with virus-variant surges, the need to learn from those past lessons to help laboratories prepare for the future is a top priority.

Lesson 1: Remind lab staff about hazards they handle every day

The initial safety training in school and on the job for laboratorians includes information about the hazards in the workplace. Handling chemical and biological agents is routine in laboratory work creating an unsafe environment for those within. However, regulatory agencies like the Occupational Safety and Health Administration (OSHA) state that employers must provide methods to mitigate those safety hazards, so employees can be safe on the job. Those safety measures can include hazard substitution, the use of engineering controls, safe work practices, and personal protective equipment (PPE). Laboratorians also are trained to use standard precautions, the idea that all specimens should be treated as if they were infectious and potentially harmful.

Over time and without regular safety awareness reminders, lab staff can become complacent about the specimens they work with each day, even if those specimens are known to be hazardous. One of the first lessons the COVID-19 pandemic taught laboratory leaders was that ongoing safety awareness is vital. When new pathogens are introduced, training can prevent unnecessary fear about the work lab employees perform every day

One of the earliest challenges brought about by the pandemic involved managing the anxieties of employees who would need to work with COVID-19 patients and specimens. The news media reported daily death tolls and, incredibly, impossible-to-determine mortality rates. (Remember: there was a lack of testing as well as asymptomatic patients who were never tested.) The specter of the unknown combined with the public and media hype created fear for many laboratorians at work. Lab employees were suddenly afraid of collecting or handling

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specimens, and healthcare workers began some unnecessary practices like double-bagging swab specimens and wearing gloves when transporting samples through clean spaces. Some laboratory staff even refused to perform COVID-19 tests, and others with direct patient contact would refuse to do their jobs.

Teaching employees to deal with those fears and to continue to do their work swiftly became a priority for lab leaders. Safety leaders were asked to conduct staff huddles and educational sessions. The purpose was to remind staff members that they typically process specimens each day that contain bacteria and other viruses that could be even more hazardous to their health and safety than the coronavirus. Each day, they may face patients who have infectious diseases of many varieties.

In the face of most pathogens, utilizing standard precautions will enable a laboratory employee to remain safe in the workplace. Looking ahead, in future pandemics, it will be helpful to remember that healthcare employees always need regular and consistent information about the proper handling of the hazards they work with and knowledge about how to remain safe on the job, even when the hazards are new.

Lesson 2: PPE should not be taken for granted

Two years ago, no one would have been able to predict a shortage of laboratory PPE. Gloves, lab coats, and even respirators quickly became items that were difficult to purchase, and in-stock supplies were at much lower levels than seen in the past. Some labs purchased whatever supplies they could find, even if they did not meet current safety standards. Other organizations bought large stockpiles of PPE when they could find it, and this created storage issues in some locations. Other problems arose as well. Some hospitals bought reusable lab coats, for example, but they did not have a laundry facility in which to wash them. The initial lesson here is to make sure a laboratory safety representative is involved in these purchasing decisions. The purchasing department may be trying to make fast decisions in these situations in the future, but there are many lab- and safety-specific considerations, and it will be important to have the proper representation on the decision-making team.

As the PPE shortages grew more severe, the Centers for Disease Control and Prevention (CDC) created new guidance for both the extended use and reuse of certain protective equipment. These references offer a lasting resource if labs face future PPE shortages. The CDC provides instructions for handling shortages of lab coats, face protection, and even gloves. The actions to take depend on the situation and the severity of the shortage. For example, N95 respirators can be used multiple times in a single day or for successive days (provided they do not get wet). They can be placed in a clean bag and reused. That was not a usual practice before the pandemic began, but it became difficult to obtain these respirators and many labs did, indeed, use them more than one time before disposal.

Other practices that were seen as the pandemic progressed included PPE reprocessing and disinfection. Many hospitals instituted disinfection protocols using ultraviolet light or hydrogen peroxide vapors to sterilize gowns and respirators for reuse. In some cases, facilities were able to conduct the disinfection on-site, and other organizations hired contractors to perform the work. It was an expensive and sometimes complex undertaking, but it was necessary to provide healthcare staff members with the items needed to continue to safely perform their work.

Finally, some laboratories and hospitals moved from using disposable items (like lab coats) to reusable ones. With costs for disposable lab coats rising and availability dwindling, it made sense for some labs to switch to a coat purchase or rental program. That meant finding a laundry service and changing the way labs handle coats, but in the long run, it would prevent running out of the coats.

As laboratories prepare for the next pandemic wave or the next potential disaster that affects PPE supplies, leaders need to ensure that the lab has a backup plan for these critical safety materials. Consider how PPE reuse or reprocessing could be used and implemented quickly. Review the extended use guidelines to make sure the lab can follow them if necessary. Labs should make the transition today to reusable PPE, so they do not need to make the change in haste when the need suddenly arises.

Lesson 3: The unsafe acts of others can affect the entire team

While the COVID-19 pandemic roared through the country, the public became keenly aware of how the unsafe acts of one person could affect them in a negative way. If a sick individual did not wear a mask, or if they did not keep distant, there was a greater potential of spreading the virus to others. Many were willing to "coach" those who would not conform to the publicly recommended safety practices. The realization that an individual's safety may be endangered has empowered some to speak up to protect themselves. This is a lesson many laboratory safety leaders would like to see in the workplace.

The unsafe behaviors that often occur in the laboratory — the lack of PPE use, having food in the department, or using cell phones — is certainly unsafe for the perpetrator, but it can also potentially have negative consequences for co-workers. A relaxed approach to safety in one area typically indicates a lack of concern in others. Pathogens can cause infections, accidents can happen, and valuable lab team members can be hindered from working due to those consequences of unsafe practices. Moving forward, it is imperative that ongoing lab safety training includes empowering lab employees to coach team members when they see unsafe acts at work, and it is equally important that leadership supports and models these behaviors.

Moving Forward

These three safety lessons are just some of the lessons learned over the past several months as laboratorians around the world strove to continue to produce quality patient results in the midst of fears of the unknown, product shortages, and ongoing personal and staffing crises. No one can predict what may come next. Coronavirus variants may continue, or the virus may become seasonal like the influenza virus. An entirely different pathogen may be ready to emerge to create the next pandemic. In any case, laboratories need to be ready for the effects of such events. Using the lessons from the recent past can help laboratories be properly prepared, so they can continue to produce quality work safely for the patients they serve around the world.

Dan Scungio, MT (ASCP), SLS, CQA (ASQ) has more than 25 years of experience as a certified medical tech. He was a lab manager for 10 years before becoming the laboratory safety officer for **Sentara Healthcare**, a system of 12 hospitals and more than 20 labs and draw sites in Virginia and North Caroline. As "Dan the Lab Safety Man," he provides consulting, education, and training in the U.S. and Canada.

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Global AIDS strategy within the SARS-COV-2 pandemic

By Andreas Boehmler

The HIV/AIDS crisis has been with us since the 1990s and represents one of the worst global pandemics in history with millions of lives lost. Today, nearly 1 million people die annually of HIV/AIDS, and there are nearly 2 million new infections annually, mainly in lower middle-income countries, such as in Africa.[1] The HIV/AIDS Global response has forced resource-limited settings to establish health frameworks and programs for HIV care, but challenges remain for key population groups.

A U.S. program called The President's Emergency Plan for AIDS Relief or PEPFAR was established in 2003 and represents the largest financial commitment from any nation for humanitarian aid.[2] The Office of U.S. Global AIDS under the Unites States Department of State has committed bipartisan support for more than $85 billion and saved 20 million lives in 50 countries since PEPFAR began. PEPFAR partners with multilateral organizations, such as The Global Fund, The Joint United Nations Program on HIV/AIDS (UNAIDS) and the World Health Organization (WHO). The World Health Organization is the global policy organization for developing guidelines for HIV prevention and treatment, and UNAIDS is a key partner in operationalizing those guidelines, helping countries implement them into their own HIV programs. UNAIDS works with countries on results monitoring and reporting to help track progress on defined milestones and targets, informing priorities and supporting data-driven and targeted implementation of programs.

To counter the health problem, UNAIDS, in cooperation with the WHO, have established country goals to overcome the HIV/AIDS pandemic by 2025, so AIDS can be erradicated by 2030 as part of a Global AIDS Strategy.[2] Countries are measured by what is known as the UNAIDS 95-95-95 goals, formerly known as 90-90-90 goals. The goals represent percentages of people living with HIV who know their HIV status, have been treated with anti-retroviral therapy (ART), and deemed virally surpressed or unable to infect others. As of December 2019, 81% of people living with HIV know their status, 82% who know their status are on ART, and 88% of those on ART are virally surpressed.[4] UNAIDS is chartered for providing global leadership for pandemic response, developing programatic approaches to support 95-95-95 goals, strengthening capacity for local governments to implement effective HIV/AIDS national control responses to reduce inequalities that drive the AIDS epidemic. The UNAIDS Global AIDS Strategy identifies where, why and for whom the HIV response is not working. Despite progress made, AIDS remains a global health crisis that requires continued emphasis to achieve the 2025 goals.

Empowerment of key populations

Inequalities, such as stigma, discrimination and criminalization, are the most significant factors preventing progress against HIV/AIDS and underpinning populations who avoid HIV care that results in deadly advanced HIV disease. This includes the majority of people with new infections living in vulnerable conditions that preclude access to healthcare. Central to the disparities that drive new infections and advanced HIV disease are societal and structural factors for human rights that diminish access to HIV services. Key populations of people living with HIV are those most affected by human rights disparities, which hampers their access to healthcare services. The UNAIDS Global AIDS Strategy involves empowering communities to reach key populations at the forefront of HIV/AIDS response. The strategy focuses on driving results in 10 areas at the community level: HIV prevention, HIV testing and treatment, vertical HIV transmission, community led responses, equal human rights, gender equality, emphasiz-

ing youth, fully funded HIV community response, integration of HIV services into local health-system and humanitarian settings and pandemics.

The WHO has recognized that key populations are most in need for HIV care. As a result, new guidelines for advanced HIV disease or AIDS have been establish by the WHO.[4] The WHO guidelines call for patients with CD4 counts less than 200 cells/µL to be considered at an advanced stage HIV disease. Understanding this important baseline of CD4 is critical to monitor patients for risks of opportunistic infections, such as tuberculosis (TB) and deadly respiratory infections. The revised 2017 WHO guidelines also call for baseline CD4 tests for new patients entering HIV care and for those patients who fail first or second line treatments or are re-entering HIV care. The use of CD4 testing is the gold standard method to assess immunological function or identify immunological failure.

Advancing service access, integration and scalability

Programatic partnerships are forged for implemenation to drive changes at the community level within countries with high burdens of disease. One of the most comprehensive frameworks for HIV/AIDS response has been the differentiated service delivery (DSD) network implemented by ICAP Global Health at Columbia University Mailman School for Public Health and the Coverage, Quality and Impact Network (CQUIN).[5] The ICAP DSD networks leverage care for HIV/AIDS, other infectious diseases and non-communicable diseases in more than 30 countries. The DSD framework is a foundation for advancing health access in resource limited settings and strengthening health systems in a scaleable way. The DSD network is consistent with UNAIDS Global AIDS Strategy to have impact at the community level because the program is designed for greater access to care and integrated HIV services.

Among other programs supported, ICAP provides population-based household surveys in resource limited settings to assess HIV impact within communities. Recent evidence supports unacceptably high rates for HIV among key populations, such as young women and people 20 to 30-years-old.[6] This suggests programatic gaps within communities to reach key populations, structural policy barriers for access to HIV care, and a need for client-centered approaches, such as DSD. People living with HIV have a diverse set of circumstances that necessitate an individual approach for HIV care. The DSD approach achieves flexibility for patient variations based upon what is required for a patient, where services are provided, the frequency of HIV services required, and who is providing the patient services. The DSD model has proved successful since implementation in 2017 and endorsed by partners, such as the WHO and PEPFAR.

Life threatening opportunistic diseases

The SARS-COV-2 pandemic has disrupted the progress towards meeting the 95-95-95 goals and represents another painful lesson for the extreme health disparities experienced for people living with HIV in lower middle-income countries. Lockdowns, as well as availability of testing and vaccines, have hampered health services, especially for people living with HIV and those in advanced stages of HIV.[7] Governments in African countries imposed restrictive measures that included social distancing to prevent healthcare system overcrowding and de-

pletion of medical supplies and resources.

Despite these challenges, health systems in lower middle-income countries showed resilience in overcoming decreases in HIV services in January through June of 2020, according to data provided by the Clinton Health Access Inititative 2021 mid-year report.[3] They achieved those results by using telemedicine to continue delivering essential healthcare services.[7] HIV health services, such as testing, ART administration, male circumcisions and female condoms, rebounded in the latter months of 2020. Still, there are hard to reach populations of people living with HIV in lower middle-income countries that hamper progress toward 95-95-95 goals.

Patients with HIV/AIDS are high risk when infected with SARS-COV-2, compounding health inequities for key populations and those hard to reach individuals requiring care. Fortunately, key programs for PLHIV during SARS-COV-2 pandemic, such as ART, Oral PrEP and testing, have shown resilience. This has been driven by virtual telemedicine adapted to the circumstances of COVID disruptions. Still, there are barriers and resistance that prevent full scale adoption for telemedince in lower middle-income countries.[8] Despite the challenges, health systems maintained resilience for HIV care, but restrictions have caused pronounced inequalities to healthcare access, putting hard-to-reach populations at greater risk.

The WHO has put measures in place to prioritize hard-to-reach populations with greater access to point of care testing (POC) and increased supplies of ART for patients, such as pregnant women, infants, those with advanced HIV disease and co-infections.[9] Countries in high burden HIV/AIDS settings are implementing more POC testing for diagnosis, providing up to six months of ART supply for patients and targeting those who are suspected of failing first line treatment.

The challenge for those living with HIV is not just to treat them with antiviral therapies — but to understand exactly how far their immune system has been compromised. Otherwise, they become susceptible to additional life threatening, opportunistic diseases. It is, therefore, critical that there is a way of identifying immunocomprised patients.

Identifying immunocomprised patients

Once a person is infected with HIV, the virus begins to attack and destroy a special type of white blood cell, called CD4. These cells play a major role in protecting the body from infection. Counting the number of CD4 cells in a patient's blood is the most accurate way of monitoring how well the immune system is working and predicting the progression of HIV. The WHO has taken steps to explain the importance of counting CD4 cells by issuing three new guidelines to encourage best practices, explaining under which circumstances it is essential to know a patient's cell count, as well as their viral load.[4,9,10] The stages that the WHO has established to evaluate patients are clinical stages one, two, three, and four. A patient with advanced HIV is defined as clinical stage three and four and at risk of an opportunistic fungal infection or requiring prophylactic therapies. Relying solely on clinical staging can miss 60-70% of patients with low CD4 counts, as they may not manifest clinical symptoms, leading clinicians to place them in a lower clinical stage than is warranted.[3] Used in conjunction with CD4 counts, these stages stratify patients as high or low risk for developing opportunistic infections. Patients with a cut-off above 200 cells/µL are at reduced risk, and below 200 cells/µL puts them at a higher risk for developing opportunistic infections.[4]

The gold standard: CD4 cell count

The 2016 and 2017 WHO guidelines provide guidance on the diagnosis of human immunodeficiency virus (HIV) infection, the care of people living with HIV and the use of antiretroviral drugs for treating and preventing HIV infection.[4,10] While these guidelines recommend lifelong antiretroviral therapy, regardless of CD4 cell count ("treat all policy") and analysis of viral load as the preferred monitoring approach, they also provide clear guidance on the indispensable role of CD4 in assessing baseline risk of disease progression, particularly for individuals presenting with advanced disease, decisions regarding starting and stopping prophylaxis for opportunistic infections, and prioritization decisions regarding ART initiation in settings where universal treatment is not possible. CD4 cell count measurement may also be important for people who are failing ART.

People with advanced disease are defined as those presenting to care with a CD4 count below 200 cells/µL or WHO disease stages 3 and 4. The package of care for these people should include the following:[10]

- Rapid initiation of ART (once the risk of immune reconstitution inflammatory syndrome is ruled out)
- Systematic screening for Cryptococcus antigen
- Screening and treatment for TB or isoniazid preventive treatment as indicated
- Screening for toxoplasmosis and Co-trimoxazole prophylaxis
- Intensive follow-up

Measures such as WHO guideline recommendations will continue to protect those patients under severe risk for SARS-COV-2 disruptions for care and resulting opportunistic infections if guidelines are followed.

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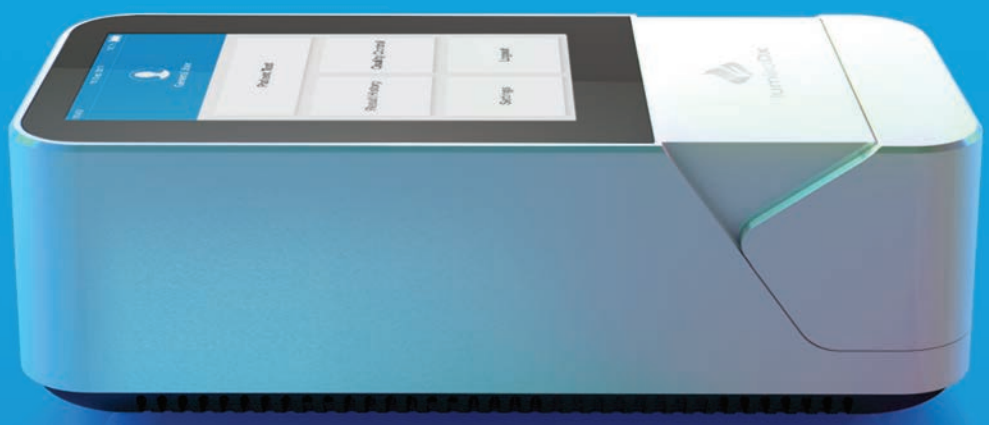

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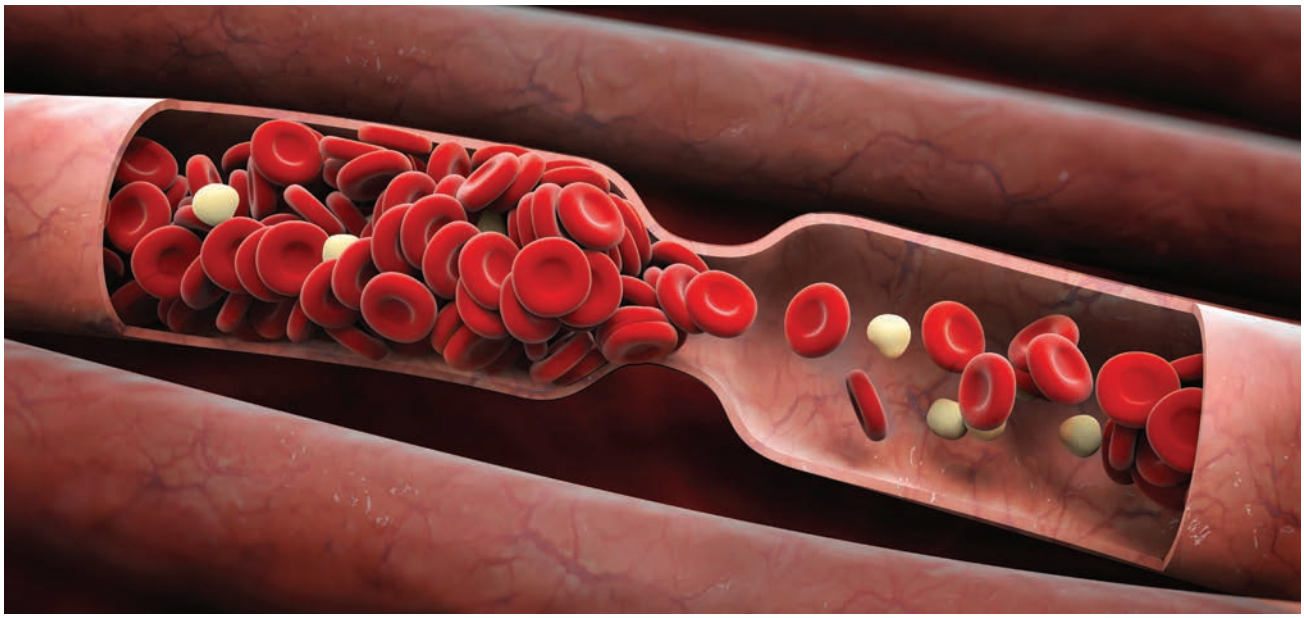

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Blood clots can kill: A current overview of thrombosis risk factors

By Paul Riley, PhD, MBA

Hellen Keller famously wrote, "Life is either a daring adventure or nothing at all." Certainly, with respect to blood flow consistently pushing throughout the body to maintain living functions, constantly changing conditions lead to a constantly risky endeavor. The need continues 24 hours per day, 7 days per week, 365 days per year, with health problems either in an acute or chronic sense, arising, even in otherwise healthy individuals.

The public at large is not fully aware of the signs and symptoms of venous thromboembolism (VTE), also known as thrombosis. A significant public health problem even before the COVID-19 pandemic, 274 people die every day as a result of blood clots just in the U.S. alone, with 100,000-300,000 deaths occurring each year, greater than the total number of people dying annually from AIDS, breast cancer and car crashes combined, according to data from the Centers for Disease Control & Prevention (CDC). Two thirds of cases occur in outpatients, with diagnostic and prescription costs between $7,594-$16,644 per patient, contributing well over $2 billion in total cost to the healthcare system annually.[1] Even if a patient survives a bout of PE or DVT, post thrombotic syndrome (PTS) occurs in up to 4-10% of these patients, causing venous insufficiency, inflammation, venous hypertension, and resulting damage to venous valves.

The level of knowledge around VTE among patients and providers could be greatly strengthened. Confusion exists even among emergency medicine providers, who may feel they cannot rely on the D-dimer assay, since they may see it more as a biomarker often elevated, especially in elderly, cancer, or obstetric patients. Public awareness of the dangers of VTE is also low, and people may not recognize the signs and symptoms, including chest pain, which gets worse as you inhale, until it is too late, and the blood clot has negatively impacted lung function.

VTE includes dangerous cases of pulmonary embolism (PE), or blood clots in the lungs; or deep venous thrombosis (DVT), often found in lower extremities, especially the lower venous system. A major contributor to morbidity and mortality, PE and DVT significantly impact the overall healthcare system, but opportunities currently exist to properly use laboratory diagnostic and clinical algorithmic tools to conserve healthcare spending while also optimizing patient outcomes.

Rudolph Virchow, a pathologist in the mid-1800s, initially characterized the VTE disease state along with many of the risk factors, publishing a description of blood clots in 1859, which he called "Embolia." The underlying risk factors of VTE were later categorized by other clinical scientists into Virchow's triad, with three different categories: (1) circulatory stasis, or overall blood movement; (2) vascular wall injury, including trauma or surgery; and (3) hypercoagulable state, such as malignancy, but also pregnancy and the peripartum period.

Importance of the D-dimer test

The COVID-19 pandemic has put a spotlight on venous and arterial thrombotic risk due to the viral disease arising from SARS-CoV-2 resulting in increased thrombotic risk. Individual patients can develop VTE in many sites throughout the body, contributing to the mortality and morbidity picture of COVID-19. Laboratory tests not only help clinicians with diagnosis and staging of viral load, but by use of the automated D-dimer test, mostly available on demand as a routine assay, providers will be able to glean information on potential patient outcomes, depending on the result. Indeed, the recently updated guideline from the International Society on Thrombosis and Haemostasis (ISTH) outlines the importance of D-dimer to identify potential thrombotic issues in COVID-19 patients presenting to the intensive care unit (ICU). According to the ISTH guideline,

Thrombophilic defect	Prevalence in the General Population (%)	Prevalence in a VTE cohort (%)	Annual VTE Risk (% / year)
Antithrombin (AT) deficiency	0.02	0.5	1.1
Protein C deficiency	0.15	6	0.7
Protein S deficiency	0.1	2	0.3
FVL heterozygosity	5	16	0.5
FVL homozygosity	0.004	0.01	1.3
Prothrombin G20210A heterozygosity	2	7	0.4
Prothrombin G20210A homozygosity	0.1	2	1.1
FVL / Prothrombin G20210A compound heterozygosity	0.1	3	0.5

Table 1: Thrombophilic defects in the general population, with prevalence and annual VTE risk[5] Source: Colucci G, Tsakiris D. Thrombophilia screening revisited: an issue of personalized medicine. J Thromb Thrombolysis. 2020; 49(4): 618–629. doi: 10.1007/s11239-020-02090-y.

COVID-19 patients exhibit not only D-dimer elevations, but also elevated fibrinogen and factor VIII, and shortened activated partial thromboplastin time (aPTT).

Published studies have consistently shown COVID-19 patients with elevated D-dimer (> 4.0 µg/mL) have poor overall outcomes, but confirmation of VTE in these patients is difficult due to patient instability or the protocol of a prone position in acutely ill patients. Regardless, use of the IMPROVE VTE score, a clinical algorithm intended for VTE identification in hospitalized patients, along with D-dimer levels > 2 times upper limit of normal (ULN) identified patients with greatly increased VTE risk, who could benefit from extended duration prophylactic anticoagulation.[2] Thus, the D-dimer assay is useful not only to exclude VTE presence in suspected patients, but also for monitoring ongoing status in at-risk, critically ill patients with COVID-19.

The use of D-dimer in COVID-19 in hospitalized COVID-19 patients reflects its well-established use in hospitalized DIC patients, along with other fibrin related markers, decreased fibrinogen, decreased platelet count, and increased prothrombin time (PT).[3] Adding to the COVID-19 laboratory testing picture, individuals suspected of Thrombosis with Thrombocytopenia Syndrome (TTS), have sometimes been observed in individuals receiving the COVID-19 vaccine up to 4-28 days prior to presentation. Those patients also show D-dimer elevations, along with changes in platelet count, aPTT, PT, fibrinogen, with confirmation using separate heparin-induced thrombocytopenia (HIT) assays.[4]

Going back to use of D-dimer in non-COVID-19 related VTE, automated high sensitivity immunoturbidimetric D-dimer assays are used in concert with a pretest probability (PTP) score (e.g., Wells Score, Geneva Score, YEARS Algorithm). D-dimer is an antigenic fragment reflective of recent fibrinolytic activation and fibrin clot presence in the plasma with the value of the assay lying in its high negative predictive value (NPV) to rule out PE and DVT. With relatively nonspecific symptoms, the test aids clinical decision making for clinicians examining patients presenting in emergency departments (ED) and urgent care facilities.

D-dimer tests available commercially are usually validated with a cutoff value of 0.50 µg/mL Fibrinogen Equivalent Units (FEU) for exclusion of PE or DVT, in concert with the PTP. Some available assays report in different units, such as ng/mL, or even in units corresponding to different defined breakdown products, D-dimer units (DDU). Alternative cutoffs may need to be considered for D-dimer use in other acute illnesses, including COVID-19 and disseminated intravascular coagulation (DIC), but institutions rarely report out validated results other than for VTE exclusion.

Clinical algorithmic tools

Various PTP scores have been established and validated in large clinical trials relating patient symptomology to outcomes, and include the Wells Score, Geneva Score, and YEARS algorithm. The different algorithms have slightly different criteria, but providers in North America generally use the Wells Score. Both clinical guidelines and assay platform manufacturers recommend utilization of a PTP in concert with a D-dimer test. The Wells Score can be programmed into the hospital information system as part of a required procedure when ordering laboratory D-dimer, establishing clinical history including active cancer, localized tenderness, recent paralysis or bedridden status, leg swelling, elevated heart rate, hemoptysis, and previous DVT/PE. In a real-world sense, other environmental or lifestyle, dietary (e.g., supplements), health, and genetic factors are important to overall thrombosis or bleeding risk, but the Wells Score depends on clinical history presented to the ordering physician at the bedside. Depending on the outcome of the score, either a D-dimer assay is ordered to exclude PE or DVT, if the patient is found low or moderate risk, or for high-risk patients, the patient is sent directly to confirmatory imaging or ultrasound to establish presence of the clot.

Risk factors for VTE progression

Underlying inherited genetic mutations related to VTE progression include factor V Leiden (FVL), prothrombin gene mutation G20210A (PGM), deficiencies of antithrombin, protein C, or protein S. Associated prevalence and annualized VTE risks for the associated conditions potentially seen by patients visiting hospitals are described here (see **Table 1**).[5] In addition, fibrinolytic factors, though less recognized to play a role from a laboratory or provider perspective, can lead to deficiencies of fibrinolytic function, which then serve to downregulate clot breakdown, extending clot appearance in the plasma, resulting in VTE progression, and potential arterial thrombosis. Those inherited aspects of thrombotic risk are combined with acquired risk factors including advanced age, previous VTE history, cancer, obesity, and/or antiphospholipid antibody presence (leading to antiphospholipid syndrome), increasing overall thrombosis risk.

These single or multiple hits, when combined with triggering events, such as estrogen therapy or oral contraception, pregnancy, surgery, or immobilization, will take the patient across the positive threshold, resulting in DVT or PE, or arterial thrombosis leading to transient ischemic attack (TIA), stroke, or heart attack.

Analysis of Medicare records in post-menopausal women showed overall post-VTE mortality was 8% at 28 days, and 22% at 1 year, largely driven by underlying comorbidities. In addition, African American women analyzed in the study showed higher VTE incidence compared to other populations, which was consistent with other studies.[6]

Overutilization of imaging studies

To examine clinician practices around D-dimer testing utilization, while simultaneously assessing the population health impact of CTPA overutilization across large health systems with varied site sizes and patient populations, a large cross-sectional analysis of ED patients in 27 different hospitals who previously underwent PE diagnostic imaging. Takeaway points from the study included the following:

- Institutional use of imaging procedures vary widely across different hospital sites, but a focus on quality improvement can improve CTPA yield rates.
- Due to higher utilization in women and at the ages shown in the study, on a population basis, they are at more risk from radiation exposure from CTPA procedures.
- D-dimer and PTP use directly correlates to improved PE yield rates, showing the important role of D-dimer at reducing unnecessary imaging procedures.[7]

The findings have clear implications for proper utilization of D-dimer testing across the healthcare system, and the findings will inform laboratory staff interested in developing local best practices. Given the study findings, clinician uncertainty around D-dimer testing should reduce once recognition of the importance of D-dimer in the care pathway are recognized.

Instead of following the PTP score and using D-dimer assays in patients with low to moderate probability to risk stratify patients, clinicians often skip the D-dimer and go directly to imaging, or simply run D-dimer and confirmatory imaging in all suspected patients, leading to unnecessary imaging procedures. Overuse of expensive and time-consuming imaging procedures, such as computed tomography pulmonary angiography (CTPA) is associated with significant population cancer risk from exposure to radiation. In addition, patients sometimes experience unexpected kidney injury from contrast nephropathy, and ambiguous or false-positive imaging results complicate management.

CTPA utilization has shown overall increases in U.S. hospitals, while concomitant PE diagnostic yield or the effectiveness of confirming diagnosis by CTPA has fallen, most likely due to improper utilization of D-dimer and PTP.[8] Indeed, a recent publication summarizing interviews with 23 clinical providers in two states indicated main barriers to proper utilization of imaging techniques included limited use, distrust, or lack of knowledge on use of institutional-based clinical decision support (CDS) tools, such as use of Wells Score and D-dimer testing.[9] Further, in the emergency department (ED) setting, approximately 5% of all patients have a test for VTE, and the median age of persons tested for PE in the ED is 46-years-old. Radiation exposure presents a significant risk later in life, especially in the case of women, but the PE positivity rate for patients tested is less than 5%, so given the increased risk inherent in the procedure, the PE positivity rate is low.[10]

Treatment of VTE is commonly performed by prescribing anticoagulants, provided either parenterally (intravenous or subcutaneous) for hospitalized patients, or in oral form in outpatients. Many parenteral and oral anticoagulant choices are now available for patients and providers to customize therapy, so treatment is greatly accessible with well-known safety outcomes.

On the bright side, not including the impact from the pandemic, overall trends had appeared positive with regards to PE incidence and outcomes in the United States, with one study of approximately 810,000 Medicare patients over 65-years-old, from 1999-2015 with a PE as their principal condition on discharge, showing decreases in case fatality rates from 8.7% to 4.0% and decreased adjusted 30-day case fatality rate from 12.7% to 9.4%, along with a decreased hospitalization rate.[11] Thus, PE care trends have been favorable, due to increased physician education and spreading of best practices across integrated delivery networks (IDNs). In any event, laboratorians must keep their colleagues on front lines of care informed to make sure the importance of VTE prevention is well understood, and the role of the lab D-dimer assay is clearly established.

Note:

To ensure patients and the public increase their level of understanding of the dangers of VTE, the International Society on Thrombosis and Haemostasis (ISTH) started an annual education and awareness day called World Thrombosis Day (WTD), taking place each year on October 13.

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Recent FDA EUAs for COVID-19 testing

EUA Issued / Updated	Entity	Diagnostic	Attributes	Authorized Setting(s)
7/1/2021	Abbott Molecular Inc. https://www.molecular.abbott/int/en/alinity-m-resp-4-plex-assay	Alinity m Resp-4-Plex	Real-time RT-PCR, Multi-analyte	H, M
8/18/2021	Abbott Molecular Inc. https://www.molecular.abbott/int/en/alinity-m-sars-cov-2-assay	Alinity m SARS-CoV-2 assay	Real-time RT-PCR, Pooling, Screening	H, M
7/28/2021	Access Genetics, LLC http://www.access-genetics.com/	OraRisk COVID-19 RT-PCR	Real-time RT-PCR	H
5/4/2021	Agena Bioscience, Inc. https://www.agenabio.com/products/panel/coronavirus-sars-cov-2-variant-detection-research-panel/	MassARRAY SARS-CoV-2 Panel	RT-PCR, chip array and MALDI-TOF Mass Spec.	H
6/8/2021	Applied BioCode, Inc. https://www.apbiocode.com/sars-cov-2.htm	BioCode SARS-CoV-2 Assay	RT-PCR, Pooling	H
7/21/2021	Applied DNA Sciences, Inc. https://adnas.com/dxcovid/	Linea COVID-19 Assay Kit	Real-time RT-PCR, Serial Screening	H
6/23/2021	BillionToOne, Inc. https://billiontoone.com/covid-19/	qSanger-COVID-19 Assay	Sequencing	H
6/17/2021	BioFire Defense, LLC https://www.biofiredx.com/covid-19/	BioFire COVID-19 Test	RT, Nested multiplex PCR, Pooling	H, M
6/29/2021	BioGX, Inc. https://biogx.com/xfree/	BioGX Xfree COVID-19 Direct RT-PCR	Real-time RT-PCR	H
6/22/2021	Biomeme, Inc. https://info.biomeme.com/covid-19	Biomeme SARS-CoV-2 Real-Time RT-PCR Test	Real-time RT-PCR, Pooled Serial Screening - Swab, Media	H
5/6/2021	Bio-Rad Laboratories, Inc. https://www.bio-rad.com/en-us/product/reliance-sars-cov-2-flu-flu-b-rt-pcr-assay-kit?ID=QKWS6LTU86LJ	Bio-Rad Reliance SARS-CoV-2 RT-PCR Assay Kit	Real-time RT-PCR	H
8/13/2021	CENTOGENE US, LLC https://www.centogene.com/covid-19/testing/about-the-sars-cov-2-test.html	CentoSure SARS-CoV-2 RT-PCR Assay	Real-time RT-PCR, Screening	H
6/24/2021	Clinical Enterprise, Inc. https://www.eurofinsus.com/	Clinical Enterprise SARS-CoV-2 RT-PCR Assay	Real-time RT-PCR, Screening, Pooled Serial Screening - Swab	H
6/24/2021	Clinomics USA Inc. http://clinomics.com/en/covid19	Clinomics TrioDx RT-PCR COVID-19 Test	Real-time RT-PCR	H
7/22/2021	DiaSorin Molecular LLC https://molecular.diasorin.com/us/kit/simplexa-covid-19-direct-kit/	Simplexa COVID-19 Direct assay	Real-time RT-PCR	H, M
7/16/2021	Enzo Life Sciences, Inc. https://www.enzolifesciences.com/ENZ-GEN215/ampiprobe-sars-cov-2-assay-kit/	AMPIPROBE SARS-CoV-2 Test System	Real-time RT-PCR, Pooling	H
7/28/2021	GenMark Diagnostics, Inc. https://genmarkdx.com/panels/eplex-panels/respiratory-pathogen-panel/	ePlex Respiratory Pathogen Panel 2	RT-PCR and electrochemical detection, Multi-analyte	H, M
7/23/2021	Hologic, Inc. https://www2.hologic.com/pantherfusion-sars-cov-2	Panther Fusion SARS-CoV-2 Assay	Real-time RT-PCR, Pooling, Screening	H
7/22/2021	Hologic, Inc. https://www.hologic.com/hologic-products/diagnostic-solutions/hologic-sars-cov-2-assays	Aptima SARS-CoV-2 assay	TMA, chemiluminescent, Pooling, Screening	H
8/18/2021	INVITES BIOCORE CO., LTD. http://www.bio-core.com/biocore/kr/common/Brochure_(ENG).pdf	BioCore 2019-nCoV Real Time PCR Kit	Real-time RT-PCR	H
7/14/2021	ISPM Labs, LLC dba Capstone Healthcare https://capstonehealthcare.com/covid19-testing/	Genus SARS-CoV-2 Assay	Real-time RT-PCR	H
7/15/2021	KimForest Enterprise Co., Ltd. https://www.kimforest.com/index.php?action=medicine&lang=3	KimForest SARS-CoV-2 Detection Kit v1	Real-time RT-PCR	H
8/2/2021	Life Technologies Corporation (part of Thermo Fisher Scientific) https://www.thermofisher.com/us/en/home/life-science/pcr/real-time-pcr/real-time-pcr-reagents/taqman-real-time-master-mixes.html	TaqPath COVID-19 MS2 Combo Kit 2.0	Real-time RT-PCR	H

COVID-19 tests continued on 38

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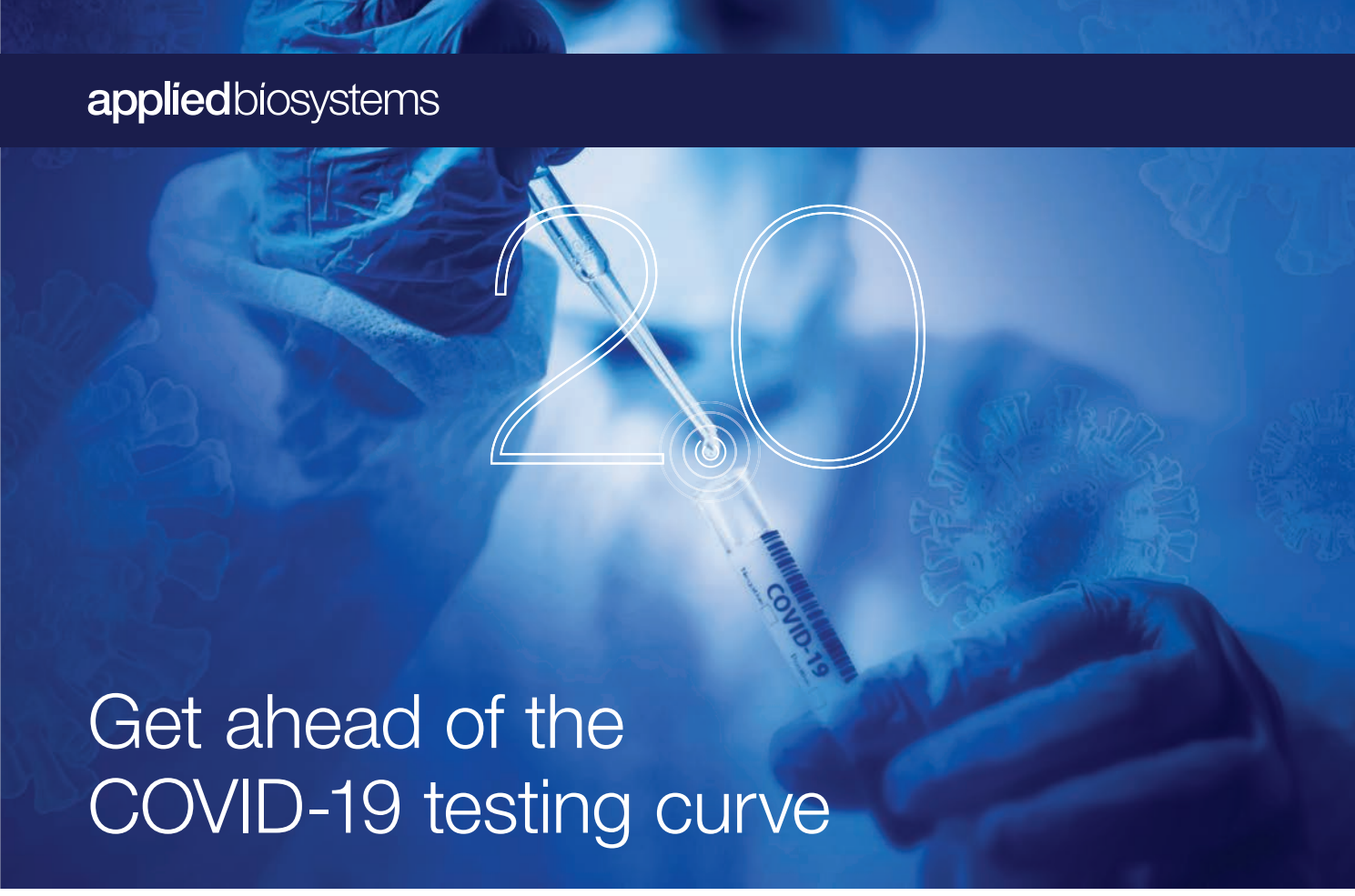

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COVID-19 tests continued from page 36

EUA Issued / Updated	Entity	Diagnostic	Attributes	Authorized Setting(s)
7/30/2021	Life Technologies Corporation (part of Thermo Fisher Scientific) https://www.thermofisher.com/us/en/home/clinical/clinical-genomics/pathogen-detection-solutions/covid-19-sars-cov-2/taqpath.html	TaqPath COVID-19 Fast PCR Combo Kit 2.0	Real-time RT-PCR, Saliva	H
3/29/2021	LumiraDx UK Ltd. https://www.lumiradx.com/us-en/what-we-do/diagnostics/fast-lab-solutions/rna-star-complete	LumiraDx SARS-CoV-2 RNA STAR Complete	RT, qSTAR amplification	H
6/17/2021	MobileDetect Bio Inc. https://mdbio.com/	MobileDetect Bio BCC19 (MD-Bio BCC19) Test Kit	RT-LAMP	H, M
6/24/2021	OSANG Healthcare http://www.osanghc.com/en/home_en/	GeneFinder COVID-19 Plus RealAmp Kit	Real-time RT-PCR	H
7/22/2021	PathogenDx, Inc. https://pathogendx.com/detectx-2/	DetectX-Rv	RT-PCR, DNA Microarray Hybridization	H
7/15/2021	PerkinElmer, Inc. https://perkinelmer-appliedgenomics.com/home/products/new-coronavirus-2019-ncov-nucleic-acid-detection-kit/	PerkinElmer New Coronavirus Nucleic Acid Detection Kit	Real-time RT-PCR, Pooling, Screening, Saliva	H
8/19/2021	PlexBio Co., Ltd. https://www.plexbio.com/intelliplex%E2%84%A2-sars-cov-2-detection-kit	IntelliPlex SARS-CoV-2 Detection Kit	RT-PCR	H
7/29/2021	QIAGEN GmbH https://qiastat-dx.com/na/	QIAstat-Dx Respiratory SARS-CoV-2 Panel	Real-time RT-PCR, Multi-analyte	H, M
5/25/2021	Quidel Corporation https://www.quidel.com/molecular-diagnostics/lyra-direct-sars-cov-2-assay	Lyra Direct SARS-CoV-2 Assay	Real-time RT-PCR	H
6/17/2021	Roche Molecular Systems https://diagnostics.roche.com/us/en/products/params/cobas-sars-cov-2-influenza-a-b-nucleic-acid-test.html	cobas SARS-CoV-2 Nucleic acid test for cobas Liat System (cobas SARS-CoV-2)	Real-time RT-PCR, Screening	H, M, W
6/24/2021	Roche Molecular Systems, Inc. https://diagnostics.roche.com/us/en/products/params/cobas-sars-cov-2-influenza-a-b-test.html	cobas SARS-CoV-2 & Influenza A/B Nucleic Acid Test for cobas Liat System	Real-time RT-PCR, Multi-analyte	H, M, W
6/8/2021	Roche Molecular Systems, Inc. https://diagnostics.roche.com/us/en/home.html	cobas SARS-CoV-2 & Influenza A/B	Real-time RT-PCR, Multi-analyte	H, M
4/15/2021	Seegene, Inc. https://www.seegene.com/assays/allplex_2019_ncov_assay	Allplex 2019-nCoV Assay	Real-time RT-PCR	H
4/30/2021	SML GENETREE Co., Ltd. https://www.smlgenetree.com/ezplex-sars-cov-2-g	Ezplex SARS-CoV-2 G Kit	Real-time RT-PCR, Pooling	H
7/8/2021	Thermo Fisher Scientific Inc. https://www.thermofisher.com/us/en/home/clinical/clinical-genomics/pathogen-detection-solutions/amplitude-solution.html	TaqPath COVID-19 RNase P Combo Kit 2.0	Real-time RT-PCR, Serial Screening	H
6/25/2021	Trax Management Services Inc. https://traxconnects.com/	PhoenixDx SARS-CoV-2 Multiplex	Real-time RT-PCR	H
6/25/2021	Twist Bioscience Corporation https://www.twistbioscience.com/resources/product-sheet/sars-cov-2-ngs-assay-ruo-product-sheet	SARS-CoV-2 NGS Assay	Sequencing	H
6/24/2021	Vela Operations Singapore Pte Ltd https://www.veladx.com/product/qpcr-respiratory-viruses/virokey-sars-cov-2-rt-pcr-test.html	ViroKey SARS-CoV-2 RT-PCR Test	Real-time RT-PCR	H
7/8/2021	Vela Operations Singapore Pte. Ltd. https://www.veladx.com/product/qpcr-respiratory-viruses/virokey-sars-cov-2-rt-pcr-test-v2.html	ViroKey SARS-CoV-2 RT-PCR Test v2.0	Real-time RT-PCR	H
6/23/2021	Viracor Eurofins Clinical Diagnostics https://www.eurofins-viracor.com/clinical/test-menu/8300-coronavirus-covid-19-sars-cov-2-rt-pcr/	Viracor SARS-CoV-2 assay	Real-Time RT-PCR, Pooling, Screening, Pooled Serial Screening - Swab	H

Abbreviations used: H - High complexity, M - Moderate complexity, W - CLIA waiver

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The administration's plans for combating COVID-19

By Marisa L. Williams

As part of an executive plan to try to pull the country out of the COVID-19 pandemic, President Joe Biden is implementing a strategy to increase vaccinations,[1] while trying to prevent lockdowns.

Since the president announced vaccination requirements for the federal government in July, encouraging the private sector to increase vaccinations, many employers, schools, nursing homes, restaurants, and healthcare facilities have announced vaccination requirements. Since May, those 12-years-old and older can get vaccinated at more than 80,000 locations nationwide.

Though more than 175 million Americans are fully vaccinated, nearly 80 million people who are eligible are not vaccinated.

Making COVID-19 testing available for all

To mobilize the industry, President Biden plans to accelerate the production of COVID-19 rapid tests, including at-home tests, to ensure manufacturers prioritize the creation of these products to prevent the spread of COVID-19 and its variants.

Using authorities of the Defense Production Act and through the procurement of nearly $2 billion in rapid point-of-care and over-the-counter at-home COVID-19 tests, approximately 280 million tests, the administration will ensure a broad, sustained industrial capacity for COVID-19 test manufacturing.

Tests are needed to support a variety of places, such as long-term care facilities, community testing sites, homeless shelteres, prisions, jails, and many other settings. Retailers like Walmart, Amazon and Kroger will offer COVID-19 tests at cost for the next three months to make testing more affordable and accessible, a discount of about 35%.

Meanwhile, Medicaid will cover at-home tests for free for beneficiaries, and states need to ensure tools used to manage at-home testing do not establish barriers for people seeking care.

Additionally, 25 million free at-home rapid tests will be sent to 1,400 community health centers and hundreds of food banks to ensure people have access to free tests. The administration is expanding the number of retail pharmacies offering anyone free testing through government's free testing program.

Mandatory vaccinations for work

The Department of Labor's Occupational Safety and Health Administration (OSHA) is developing a rule that will require all employers with 100 or more employees to ensure their workforce is fully vaccinated, or require any workers who remain unvaccinated to produce a negative test result on at least a weekly basis before coming to work. OSHA will issue an Emergency Temporary Standard (ETS) to implement this requirement, and this will impact more than 80 million workers.

The Centers for Medicare & Medicaid Services (CMS) is requiring COVID-19 vaccinations for workers in most healthcare settings that receive Medicare or Medicaid reimbursement, from hospitals and dialysis facilities to ambulatory surgical settings, home health agencies, and more. This will apply to nursing home staff, as well as staff in hospitals and other CMS-regulated settings, including clinical staff, individuals providing services under arrangements, volunteers, and staff who are not involved in direct patient, resident, or client care. These requirements will apply to approximately 50,000 providers.

Meanwhile, OSHA is developing a rule to require employers with more than 100 employees to allow paid time off for workers to get vaccinated or to recover from any adverse reactions from receiving the vaccination.

Keeping the public safe

In places of large gatherings, such as entertainment venues, sports arenas, and concert halls, the president is calling for proof of vaccination or a negative test prior to entry. Health officials are also planning the rollout of booster vaccinations starting on September 20, 2021. Information will be available on Vaccines.gov, including what vaccines are available at each site, as well as open appointment times. People can call 1-800-232-0233, utilize WhatsApp, or use the text code 438829 to receive vaccine and booster information.

The president hopes these attempts will help keep schools open, along with universal indoor masking, maintaining physical distance, improving ventilation and screenings. More than half of the nation's adolescents have been vaccinated. The Centers for Disease Control and Prevention (CDC) found that the rate of hospitalization for children was nearly four times higher in states with the lowest vaccination rates, compared to states with high vaccination rates. The plan calls for governors to require vaccinations for teachers and school staff.

Transportation Security Administration (TSA) expanded its orders for air and ground travel through January 18, 2022, doubling fines for people who are not compliant with wearing masks in airports and while on public transportation. Physical distancing and mask wearing is also required at all federal buildings, federal land, and military bases.

The Department of Defense will double its clinical teams deployed to support hospitals with surges of COVID-19 cases. Free monoclonal antibody treatments are also being shipped to facilities around the country, with about 100,000 doses shipped per week in July and August. The Department of Veterans Affairs opened up more than 150 hospital facility beds in surge states in attempt to lessen the burden on local hospitals.

Supporting economic recovery

The COVID Economic Injury Disaster Loan (EIDL) program provides long-term, low-cost loans to small businesses. The maximum funding has been increased to $2 million, instead of $500,000, and this money can be used to hire and retain employees, purchase inventory and equipment, as well as pay off higher-interest debt. Repayment begins two years after the funding is received.

The Small Business Administration has made more than $11 million in loans that can be forgiven if the money is used to keep employees on payroll, and the loan is $150,000 or less. Borrowers spend an average of six minutes on the application, and 60% of applicants complete the process on their mobile phone.

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The impact of the COVID-19 Pandemic on Oncology

By Lisa-Jean Clifford

The entire healthcare community is painfully aware of the impact that the COVID-19 pandemic has had on patients, staff, healthcare facilities, capacity, and supplies. The effect on laboratories has been two-fold. First, the shutdown of many essential and non-essential services and procedures had a direct impact on general laboratory testing volumes, putting many businesses in a very difficult position financially. Second, the demand for new testing to support the needs of COVID-19 diagnosis and treatment had laboratories that were forward-thinking, scrambling to retrofit their equipment, reagents, test supplies, and operations to support the demand. While this had a positive financial impact for those facilities, it also directly impacted their resources to support their standard test menus and processes.

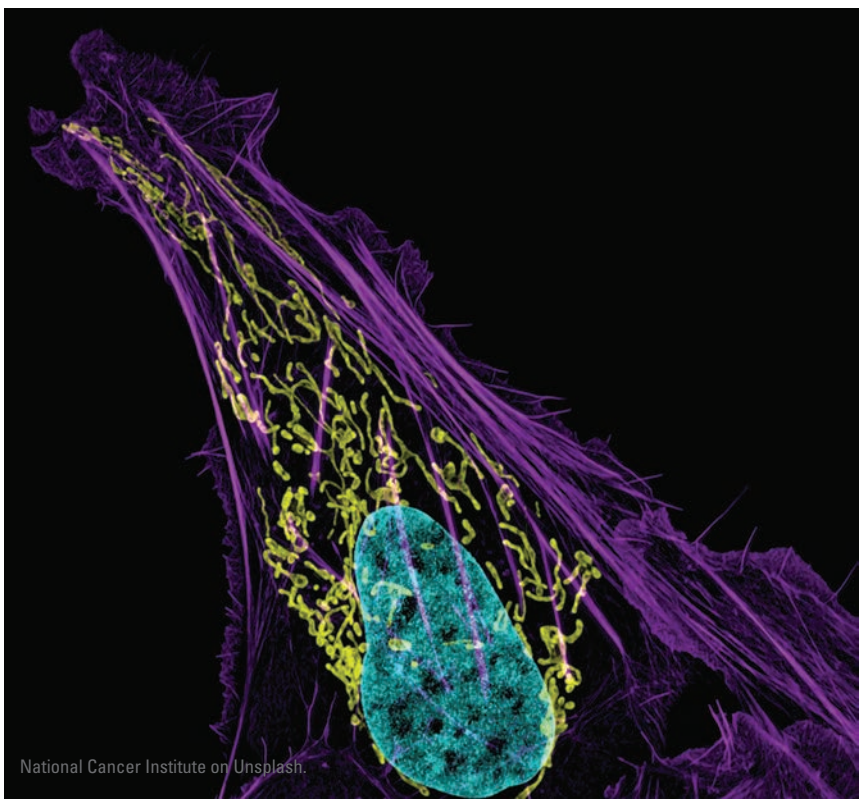

Image of a cancer cell. The COVID-19 pandemic delayed diagnosis and treatment for cancer.

Oncology was one of the medical service lines impacted by the pandemic. The pandemic — including the shutdown of all non-essential services — has had a devastating impact on oncology screening, testing, biopsies, surgeries, diagnosis, and treatment for patients in the United States. The long-term effects are as yet unknown, but certain presumptions can be made based upon the data.

For a person who has new symptoms, or needs to begin the screening process, the impact has been catastrophic. A survey of 356 cancer centers in 54 counties detailed the impact of the pandemic on the delivery of cancer services. The majority of centers (88%) said they had reduced the level of care. More than half said the reductions were precautionary, but others noted other reasons, such as an overwhelmed system (20%), staff shortages (18%), and lack of access to medications (10%)[1].

When asked about the potential harm to patients from the service disruptions, 46% said more than 10% of patients missed at least one chemotherapy session.[1]

Authors of another paper noted declines in new cancer diagnoses in the United States. In a research letter in *JAMA Network Open*, they analyzed de-identified data on diagnostic testing for eight cancer types from January 2018 to March 2021, based on 799,496 patients. After dividing the data into three pandemic periods (March-May 2020, June-October 2020, and November 2020-March 2021), they found a significant decline in new diagnoses of cancer in the first and third pandemic periods but not the second period.[2]

These numbers are daunting if you look at the potential impact that decreases and delays in diagnosis and treatment can have for an oncology patient. The situation can literally have a direct impact on their prognosis.

For example, in a study in *The Lancet Oncology*, researchers said that delays in diagnosis and treatment are expected to be associated with increases in mortality in the United Kingdom from breast, colorectal, and lung cancers by as much as 9.6%, 16.6%, and 5.3%, respectively, up to 5 years after diagnosis.[2] The authors attributed the delays to COVID-19 pandemic mitigation measures, such as lockdowns.[3]

How can we as a community and a profession do better? What options and solutions are available to prevent these types of disruptions, as surges in the COVID-19 pandemic occur for an unforeseen period of time? Is there anything we can do to neutralize some of the damage that has already been caused to oncology patients by these initial delays in screening, diagnosis, and treatment?

The rise of digital pathology

Digital pathology became a relevant response to safely provide access to pathologists anytime and anywhere. Digital pathology efficiently reduces the time to diagnosis and provides pathologists with access to patient case information by delivering the whole slide images electronically and in an automated, integrated environment. This helps the pathologist by providing all of the information that they need to diagnose a patient quickly and accurately, then enables the instantaneous distribution of that information back to the ordering clinician.

Efficiency gains have been seen in the 20-40% range, based upon studies done by labs that have implemented the technology.

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To facilitate the use of digital pathology during the pandemic, the U.S. Food and Drug Administration (FDA) issued a temporary order in April 2020, relaxing the requirements for the use of remote-reviewing and reporting of scanned digital images and pathology slides.[4]

The policy is in place for the duration of the pandemic, and the agency may decide to make it permanent.

The goal of the policy is to allow laboratories and pathologists to diagnose patients remotely using digital pathology and AI-assisted technologies, following specific validation processes. In the guidance, the FDA said it would not object to the alteration or modification of FDA-cleared devices or the marketing of new pathology devices for remote use.

Providing fast, timely diagnosis for a patient, and being able to send the report automatically and instantaneously to their ordering physician or oncologist, will enable patients to get into treatment plans much faster.

A relatively small number of laboratories were using digital pathology prior to the pandemic. These laboratories were able to scale their use and provide support to patients and physicians, while others realized the benefits of putting an operational plan in place to adopt digital pathology. The ability to have real-time access to patient information and pathologists, who may be working from other locations outside the lab, quickly became a prime consideration.

Laboratories that use digital pathology solutions will also be able to minimize any impact that a resurgence in COVID-19, such as the one we are currently seeing with the Delta variant, will have on the continued care for oncology patients. Implementing digital solutions now also will help labs cope with future pandemics and other states of emergency that could negatively impact the pathology workflow.

The entire workflow of the patient case (whole slide images, interpretation, and diagnosis) can all be done safely from any location when a complete, secure, and remotely accessible solution is in place. This, in addition to all the known and expected benefits of deploying digital pathology and AI solutions, is a compelling reason for healthcare entities to expedite their plans for including digital workflows in their operations in the near term. It has become obvious that planning for unforeseen events that are as negatively impactful as this pandemic is necessary, yet always 20/20 in hindsight. Lessons learned show us that being prepared, based on our current knowledge and experience, can ensure that patients, especially oncology patients, can continue to receive the screening and diagnostic healthcare that they need in a timely manner.

Artificial intelligence

Artificial intelligence (AI) algorithms are a sure way to gain ground on some of the time lost for patients by assisting pathologists in speeding up the time to diagnosis. AI algorithms for varying applications are readily available and are being developed in an increasing number of content areas. There are algorithms that can help identify abnormal cells, identify specific types of tumors, and triage cases higher in the work queue of pathologists, based upon the interpretation of a higher potential risk for positivity or complexity. Algorithms also perform mundane tasks, such as counting cells and performing calculations to determine cancer scores and severity grading. All of these are excellent tools for a pathologist to leverage, adding efficiencies that facilitate faster patient diagnosis and with greater confidence.

It is clear why the focus of technological advancements in pathology are on digital pathology, AI and image analysis, as they support a faster diagnosis and increase accuracy when combined with the professional expertise of a pathologist. As digital pathology becomes more widely adopted, we can hope for faster diagnoses, more prevalent application of personalized, targeted treatment, and better outcomes for the patient. The ability to diagnose patients while supporting the need for quarantines or social distancing among professionals who are in remote locations is a great added bonus for healthcare facilities and patients alike.

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I certify that the statements made by me above are correct and complete, Kristine Russell, Executive Vice President

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Lisa-Jean Clifford is the COO and Chief Strategy Officer at **Gestalt Diagnostics.**

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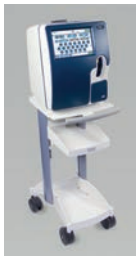

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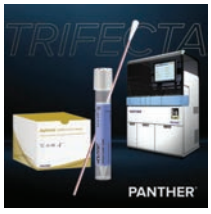

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Advancing digital pathology and informatics

By Linda Wilson

David McClintock, MD, is an Associate CMIO, Director of Digital Pathology, and Associate Director of Pathology Informatics at **Michigan Medicine**. He also is an Associate Professor of Pathology. Before joining the staff at Michigan Medicine, McClintock served in numerous roles at the University of Chicago Medicine.

Why did you decide to move from the University of Chicago Medicine — where you were the medical director of pathology informatics, among other roles — to your current positions at the University of Michigan?

I decided to move to the University of Michigan/Michigan Medicine for three main reasons:

1. While I was medical director of pathology informatics at University of Chicago Medicine, I had very little influence on decisions about informatics and central IT processes that affected the clinical laboratories. At Michigan Medicine, I would oversee a much larger, autonomous pathology IT group (pathology informatics) that has a direct impact on the operations of Michigan's clinical labs and patient care.
2. I would work with and learn from two other pathology informatics faculty members daily, which is very rare in our field, given that most institutions only have a single pathology informaticist (if they have someone at all).
3. There would be expanded educational and research opportunities for me in clinical informatics at Michigan Medicine.

Will you describe the key duties of your role as associate CMIO and how your inclusion on this team benefits the clinical laboratory and pathology department?

I am the associate CMIO (ACMIO) for pathology at Michigan Medicine (one of 15 total ACMIOs). My key duties include serving as a liaison between clinicians and our pathology informatics team, representing the Department of Pathology at enterprise informatics/IT meetings, and acting as the primary contact for information assurance/cybersecurity risk and IT compliance issues for pathology applications. The key benefit of being part of the institutional clinical informatics team is ensuring that pathology and the clinical laboratories are "at the table," and their voices are heard for major IT decisions and initiatives made on the enterprise level.

Since April 2021, the 21st Century Cures Act has required laboratories to release lab tests and pathology reports to patients promptly. What impact do you expect this requirement to have on the workflow at labs?

For most hospital labs where results are posted to the electronic health record (EHR) and its patient portal, there was little impact with Information Blocking Phase 1 since the primary burden was on EHR teams. That said, with Information Blocking Phase 2 (December 2021-December 2022), all ancillary clinical applications containing electronic protected health information (ePHI) will now be expected to have their data included in responses to information requests. This means clinical laboratories will have to assess not only their primary laboratory information system but also all middleware and other primary lab systems (e.g., for molecular, human leukocyte antigens [HLA], outreach/reference lab, etc.) to see if information from those systems is required to be included in responses to formal information requests. This may add additional work to both the IT and lab teams if they create standardized reports to handle these requests to achieve full compliance with the 21st Century Cures Act Final Rule.

In your opinion, what are the keys to implementing a digital pathology system successfully?

There are many different ways one could implement digital pathology, but in short, the primary keys are to do the following:

1. Understand the use cases that are driving digital pathology forward at your institution.
2. Create a realistic budget for digital pathology that includes not only the whole slide imaging systems but also the storage, network, staff, workstations, displays, and additional software required.
3. Implement digital pathology in a stepwise fashion, so you can iron out any kinks in the process and evolve your laboratory and sign-out practices accordingly.

Will you describe what computational pathology is and how it can improve diagnostics and patient outcomes?

Computational pathology is best described as incorporating multiple sources of pathology and clinical laboratory data to create mathematical models that generate diagnostic inferences and predictions to make the best possible medical decisions. Over the past few years, computational pathology has become closely tied to the fields of machine learning and artificial intelligence (AI), with those terms taking over the healthcare informatics space. In general, AI, through the use of machine learning models, has the ability to improve multiple facets in pathology, from providing clinical decision support during the sign-out process to optimizing laboratory workflows. For example, current AI models show promise in standardizing diagnostic criteria for cancer synoptic reporting, creating computational "assays" to predict patient response to treatment and/or prognosis, and improving clinical laboratory operations through predictive and prescriptive analytics.

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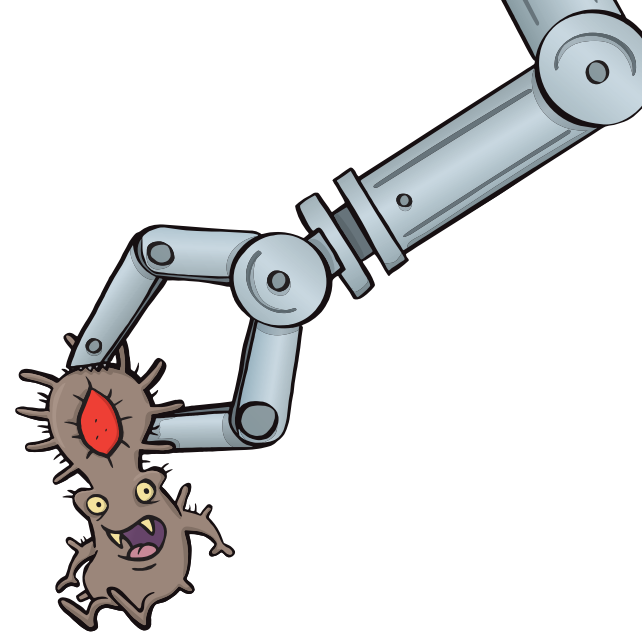

Get a grip on what's making patients sick.

Identify what you may be missing with traditional laboratory diagnostics with the BioFire® FilmArray® Gastrointestinal (GI) Panel.

Detecting and identifying gastrointestinal pathogens in a clinically actionable timeframe can be challenging for any laboratory. To further complicate diagnosis, traditional testing methods are slow, insensitive, and may not accurately identify what enteric pathogen could be making a patient sick. Fortunately, the BioFire GI Panel tests for 22 of the most common GI pathogens—increasing pathogen identification—in about one hour. With fast, accurate, and comprehensive testing, get a better handle on what is making patients sick.

Better Testing. Better Diagnostics.

- Detected 25%–36% more potential pathogens[1-4]
- Decreased time-to-result by 84%[4]
- 2 minutes of hands-on time
- Results in about 1 hour
- Any tech on any shift

biofiredx.com/filmarraygi

BIOFIRE®
BY BIOMÉRIEUX

Syndromic Testing: The Right Test, The First Time.

1. Cybulski R, et al. Clinical impact of a multiplex gastrointestinal PCR panel in patients with acute gastroenteritis. 2018. Clin Infect Dis. 2018 Nov 13;67(11):1688-96. **2.** Spina A, et al. Spectrum of enteropathogens detected by FilmArray GI Panel in a multicenter study of community-acquired gastroenteritis. Clin Microbiol Infect. 2015 Aug;21(8)719-28. **3.** Khare R, et al. Comparative evaluation of two commercial multiplex panels for detection of gastrointestinal pathogens by use of clinical stool specimens. J Clin Microbiol. 2014 Oct;52(10):3667-73. **4.** Beal SG, et al. A gastrointestinal PCR panel improves clinical management and lowers health care costs. J Clin Microbiol. 2018 Jan;56(1):e01457-17.

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